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947. *The Oxidation of Aromatic Amines. Part V.* Oxidation by Perphosphoric Acids.*

By E. Boyland and D. Manson.

Aromatic amines are oxidised by permonophosphoric acid or a mixture of peracetic and phosphoric acid. Aniline is oxidised to *p*-aminophenol and *p*-aminophenyl dihydrogen phosphate, 2-naphthylamine to 2-amino-1-naphthol and 2-amino-1-naphthyl dihydrogen phosphate; but *NN*-dimethyl-2-naphthylamine gives its *N*-oxide, and anthranilic acid yields azoxybenzene-2 : 2′-dicarboxylic and 5-hydroxyanthranilic acid. The oxidation to phenolic derivatives does not proceed in neutral or alkaline solution, or in the absence of acetone or some other carbonyl derivatives.

Aromatic amines are oxidised by mammals to aminophenols which are excreted as sulphuric esters or glucuronides. The possibility that the oxidations were oxidative phosphorylations, yielding aminophenyl phosphoric esters, has been examined [1] but no evidence for the presence of 2-amino-1-naphthyl dihydrogen phosphate could be found on biological oxidation of 2-naphthylamine. The oxidation of aromatic amines with perphosphoric acid has been studied (*a*) because it might be analogous to the biological oxidation, (*b*) as a method of preparation of the aminophenyl phosphates as reference compounds in connection with the biological oxidation of amines, and (*c*) for comparison with oxidation by persulphate.[2] Mammals excrete phenols as sulphuric esters and, surprisingly, not as phosphoric esters although much more phosphate than sulphate is excreted.

It was expected that phosphoric esters of aminophenols would be formed by oxidation with alkaline perdiphosphate because oxidation with alkaline neutral or acidified persulphate yields *o*-aminophenyl sulphates as the main products.[2] Neither potassium nor ammonium perdiphosphate oxidised 2-naphthylamine to phosphoric esters. The production of both 2-amino-1-naphthol and its phosphoric ester by oxidation by permonophosphoric acid in the presence of acetone was seen in preliminary experiments with the mixed acids formed by the reaction of pyrophosphoric acid with hydrogen peroxide.[3] When the mixed acids were added to 2-naphthylamine in 50% aqueous acetone containing an excess of alkali, no aminonaphthol derivatives were formed at room temperature or at the boiling point. If the alkali was omitted, however, 2-amino-1-naphthol and 2-amino-1-naphthyl phosphate were produced, but only if acetone was present. As perdiphosphoric acid is stable in alkali but decomposed in acid solution, while permonophosphoric acid is stable in acid only,[3] these results suggest that the oxidation to aminophenols requires permonophosphoric acid.

Permonophosphoric acid free from perdiphosphoric acid can be prepared by treating hydrogen peroxide with phosphoric oxide in acetonitrile.[4] This material in acetone solution oxidised 2-naphthylamine to 2-amino-1-naphthol and to 2-amino-1-naphthyl dihydrogen phosphate. In aqueous acetone the yield of phosphate was greatly reduced, and in the absence of acetone or other ketones or in neutral solution no phosphate was formed. The yield was not significantly altered by changing the rate of addition of the per-acid or by varying the temperature of the reaction from −5° to the boiling point of the mixtures. Oxidation with an excess of permonophosphoric acid gave 2-carboxycinnamic acid. 2-Amino-1-naphthyl dihydrogen phosphate was also readily prepared by oxidation of 2-naphthylamine with peracetic acid in the presence of phosphoric acid and acetone. 2-Amino-1-naphthol, also produced in the oxidations, was not isolated but it was detected

* Parts I—IV, *J.*, 1953, 3623; 1954, 980; 1956, 1337; *Biochem. J.*, 1956, **62**, 546.

[1] Boyland and Manson, *Biochem. J.*, 1955, **60**, ii.
[2] Boyland, Manson, and Sims, *J.*, 1953, 3623.
[3] Schmidlin and Massini, *Ber.*, 1910, **43**, 91.
[4] Toennies, *J. Amer. Chem. Soc.*, 1937, **59**, 555.

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by the green product formed on addition of ammonia, and was extracted by benzene as a purple solution.[5] 2-Acetamidonaphthalene resisted oxidation by permonophosphoric acid or by a mixture of peracetic and phosphoric acid. *NN*-Dimethyl-2-naphthylamine with permonophosphoric acid in aqueous acetone gave the amine oxide; Auerbach and Wolffenstein [6] found that hydrogen peroxide had no effect on *NN*-dimethylnaphthylamine.

Aniline and permonophosphoric acid gave *p*-aminophenol and *p*-aminophenyl dihydrogen phosphate in the presence of acetone, but not in acetonitrile or water alone. No *o*-aminophenol was detected. Aniline and peracetic acid in the presence of phosphoric acid gave *p*-aminophenyl dihydrogen phosphate (readily isolated as the monosodium salt) and some *p*-aminophenol (not isolated). For chromatographic identification, *p*-aminophenyl phosphate was prepared by catalytic reduction of disodium *p*-nitrophenyl phosphate.

Oxidation of anthranilic acid in aqueous acetone by permonophosphoric acid gave azoxybenzene-2 : 2′-dicarboxylic acid and a small amount of 5-hydroxyanthranilic acid, but no 3-hydroxyanthranilic acid. Oxidation of 1-naphthylamine, benzidine, or 2-aminofluorene with permonophosphoric acid in acetone gave small amounts of phosphoric esters detected as slow-running amino-compounds on paper chromatograms. No 3 : 3′-dihydroxybenzidine was detected among the products of the benzidine oxidation.

Different solvents for permonophosphoric acid oxidations were investigated, the formation of 2-amino-1-naphthol and 2-amino-1-naphthyl dihydrogen phosphate being studied. The results are tabulated. Some of the solvents were compared with acetone

Solvents in which no phenolic products were formed		Solvents in which 2-amino-1-naphthol and its phosphate were formed	
Water	Chloroform	Acetone	Acetonylacetone
Acetonitrile	Pyridine	Aqueous acetone (50%)	Diacetyl
Pentyl alcohol (BS696)	Acetic acid	Ethyl methyl ketone	Et acetoacetate
Propan-2-ol	Ethyl acetate	Diethyl ketone	Pyruvic acid (10% aq.)
Ethanol	Di*iso*butyl ketone	Acetophenone	Formaldehyde (33% aq.) *
Ether	Salicylaldehyde	Benzophenone	Acetaldehyde (50% aq.) †
Dioxan		Acetylacetone	Benzaldehyde †

* Only 2-amino-1-naphthol formed. † Only the phosphate formed.

in the synthesis of the phosphoric ester on a preparative scale; ethyl methyl ketone gave a lower yield. If *N*-benzylidene-2-naphthylamine in aqueous suspension or in acetonitrile was treated with the per-acid, 2-amino-1-naphthyl phosphate was formed. From these results it appears that carbonyl derivatives facilitate the oxidation.

The formation of compounds between the permonophosphoric acid and acetone was investigated by comparing solutions in acetonitrile and in acetone on paper chromatograms. The acetone solution showed two spots which were not present in the acetonitrile solution: one (R_P 0·5) gave a positive reaction for phosphate ion and for oxidising activity: the other (R_P 0·85) consisted of an oxidising substance which gave no phosphate reaction. Neither of these spots was obtained if acetone was treated with hydrogen peroxide only. If an acetone solution of the per-acid was kept for two days at room temperature the per-acid disappeared, but the products giving the spots described above remained and the solution was still capable of oxidising 2-naphthylamine to 2-amino-1-naphthol and its phosphoric ester.

Horner and Schwenk [7] proposed mechanisms for the reaction of benzoyl peroxide with aniline, methylaniline, and dimethylaniline: the postulated primary step is a transfer of one electron from the unshared pair of the nitrogen atom to one of the peroxidic oxygen atoms, resulting in fission of the −O−O− bond and formation of a radical and a negative ion. A similar mechanism may account for the formation of phenols and phosphoric

[5] Liebermann and Jacobson, *Annalen*, 1882, **211**, 36.
[6] Auerbach and Wolffenstein, *Ber.*, 1901, **34**, 2411.
[7] Horner and Schwenk, *Angew. Chem.*, 1949, **61**, 411.

esters by permonophosphoric acid. The per-acid might be split by the transfer of an electron from the amino-nitrogen atom to give hydroxyl or phosphate radicals. The formation of *p*-aminophenol and 2-amino-1-naphthol and their phosphoric esters seems to occur only in the presence of a carbonyl compound. Robertson and Waters,[8] and Criegee,[9] have suggested that the oxidation of oxopolymethylenes to lactones by permonosulphuric acid (Baeyer and Villiger reaction[10]) might proceed by way of an addition compound between the carbonyl compound and the per-acid. It is also known that aldehydes and ketones react with hydrogen peroxide or hydroperoxides to give hydroxyalkyl peroxides. Doering and Dorfman[11] investigated the conversion of [^{18}O]benzophenone into phenyl benzoate by perbenzoic acid and found the results to be consistent with an initial addition of the per-acid to the ketone. Similar addition compounds may play a part in the oxidation of amines by permonophosphoric acid in the presence of carbonyl compounds. The oxidation of *NN*-dimethyl-2-naphthylamine to an amine oxide, and of anthranilic acid to an azoxy-compound, are reactions typical of hydrogen peroxide or organic per-acids.

Experimental

Paper chromatography was carried out by ascending development on Whatman no. 1 paper, with butan-1-ol–acetic acid–water [(*a*) 2 : 1 : 1 or (*b*) 4 : 1 : 5 by vol.].

Preparation of Permonophosphoric Acid.—Toennies[4] prepared the per-acid on a small scale. It was prepared safely in larger quantities provided the cooling and mixing were carefully controlled. Use of ether as a solvent on this scale (in place of acetonitrile), however, resulted in an explosion. Phosphoric oxide (14·2 g.) was suspended in acetonitrile (30 ml.) at −5°, and hydrogen peroxide (6·8 g. as 7·8 g. of 87% hydrogen peroxide; Laporte Ltd.) and water (0·8 g.) in acetonitrile (10 ml.) were added during 45 min. with stirring, so that the temperature did not rise above 10°. The mixture was kept cold for 1 hr. and then at room temperature overnight; it was stored in a refrigerator and assayed iodometrically before use as described by Toennies.[4] The yield of per-acid was 10·5 g. (46%) and 3·3 g. of hydrogen peroxide remained unchanged. On storage at 5° the per-acid and hydrogen peroxide content fell. 1 ml. of solution, containing initially 0·34 g. of H_3PO_5 and 0·04 g. of hydrogen peroxide, contained 0·21 g. of per-acid and 0·02 g. of peroxide after 26 days. Another 1 ml., containing initially 0·25 g. of per-acid and 0·06 g. of peroxide, had after three months in the cold, 0·04 g. and 0·002 g. respectively.

Oxidation of 2-Naphthylamine by Permonophosphoric Acid.—(*a*) *In acetone.* To 2-naphthylamine (7 g.) in acetone (150 ml.) permonophosphoric acid (5 g., in acetonitrile) was added dropwise with stirring during 30 min. After a further 30 minutes' stirring, the solution was made alkaline with 2N-sodium hydroxide, and most of the acetone removed under reduced pressure. Water was added and the solution extracted with ether (5 × 100 ml.), acidified with concentrated hydrochloric acid, and extracted with butan-1-ol (5 × 100 ml.). The combined butanol extracts were made alkaline with aqueous ammonia (*d* 0·88), then evaporated to dryness under reduced pressure, and the residue was dissolved in dilute ammonia solution. The solution was treated with charcoal whilst hot, filtered, and acidified with concentrated hydrochloric acid, *2-amino-1-naphthyl dihydrogen phosphate* (1·2 g.) separating. Recrystallisation by dissolution in alkali and precipitation with concentrated hydrochloric acid gave prisms, m. p. 247—249° (Found: P, 12·7; N, 5·6. $C_{10}H_{10}O_4PN$ requires P, 13·0; N, 5·9%). Hydrolysis of the ester (0·5 g.) by 5N-sulphuric acid (5 ml.) at 100° for 30 min. yielded, on cooling, 2-amino-1-naphthyl hydrogen sulphate. The *N*-benzoylbenzoate formed needles (from ethanol), m. p. and mixed m. p. 180° (Found: N, 3·9. Calc. for $C_{24}H_{17}O_3N$: N, 3·8%). The phosphoric ester gave a brick-red colour after diazotisation and coupling with hexylresorcinol. It gave a positive reaction in Wade and Morgan's phosphate test,[12] but did not respond to Hanes and Isherwood's test,[13] unlike 1-naphthyl dihydrogen phosphate. In solvent system (*a*) the ester had R_F 0·72.

[8] Robertson and Waters, *J.*, 1948, 1574.
[9] Criegee, *Annalen*, 1948, **560**, 127.
[10] Baeyer and Villiger, *Ber.*, 1899, **32**, 3625; 1900, **33**, 858.
[11] Doering and Dorfmann, *J. Amer. Chem. Soc.*, 1953, **75**, 5595.
[12] Wade and Morgan, *Nature*, 1953, **171**, 530.
[13] Hanes and Isherwood, *ibid.*, 1949, **164**, 1107.

When ethyl methyl ketone was used as a solvent in the oxidation, the yield of ester from 7 g. of amine was 0·4 g.

The ester reacted immediately as an amine with *p*-dimethylaminobenzaldehyde to give a yellow colour, and was only slowly hydrolysed by 5N-sulphuric acid at 100°.

(*b*) *In aqueous acetone.* 2-Naphthylamine (7 g.) was dissolved in acetone (100 ml.) and water (50 ml.), and per-acid (5 g.) was added during 15 min. The mixture was kept overnight and the phosphoric ester (0·1 g.) isolated as in (*a*). When the mixture was worked up 40 min. after the addition of the per-acid the yield was 0·15 g.; when the reaction was carried out at −5° and the mixture worked up after 40 min. it was 0·04 g.; after 1 hour's refluxing, it was 0·1 g.

(*c*) *Oxidation at* pH 6·0. The reaction was carried out as in (*b*) but the pH of the per-acid solution was adjusted to 6·0 by 2N-sodium hydroxide. Titration of an aliquot part indicated no loss of per-acid by this treatment. No phosphoric ester was isolated, although paper chromatography indicated that a trace was present.

(*d*) *Use of excess of per-acid in aqueous acetone.* 2-Naphthylamine (5 g.) in acetone (140 ml.) and water (70 ml.) was treated with per-acid (12 g.) and after 1 hr. the mixture extracted as in (*a*). The product (1·5 g.), isolated by the acidification of an aqueous solution of the residue from the butan-1-ol extract, had m. p. 190—192° after recrystallisation from aqueous ethanol. It was acidic, did not diazotise or couple with hexylresorcinol, and contained no nitrogen or phosphorus. It gave no depression of the m. p. with 2-carboxycinnamic acid (Found: C, 62·5; H, 4·4. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). As described by Titley [14] the melt solidified on further heating and could then be remelted at a lower temperature (140—144°; Titley reports 151°). The diamide, prepared by treatment with thionyl chloride followed by reaction with ammonia, formed needles, m. p. and mixed m. p. 201—202° (Found: N, 14·9. Calc. for $C_{10}H_{10}O_2N_2$: N, 14·7%).

(*e*) *Oxidation in acetonitrile.* 2-Naphthylamine (7 g.) was treated in acetonitrile (60 ml.) with the per-acid (4 g.) during 30 min. Working up as before yielded only 2-carboxycinnamic acid (0·05 g.) from the butan-1-ol fraction. Chromatography of this and the original reaction mixture revealed no 2-amino-1-naphthyl dihydrogen phosphate.

Oxidation of 2-Naphthylamine by Peracetic Acid in the Presence of Phosphoric Acid.—2-Naphthylamine (7 g.) and phosphoric acid (9·8 g.) were dissolved in acetone (150 ml.). 40% Peracetic acid (10 ml.) was added with stirring during 30 min. Stirring was continued for a further 1·5 hr., then the mixture was made alkaline with 2N-sodium hydroxide, and most of the acetone removed under reduced pressure. After dilution with water, the solution was extracted several times with ether, and the aqueous layer acidified, to yield the phosphoric ester (3·5 g.), m. p. and mixed m. p. 242—244° (decomp.) (*N*-benzoylbenzoate, m. p. 180°).

Oxidation of NN-*Dimethyl-2-naphthylamine.*—The amine [15] (5 g.) in acetone (100 ml.) and water (50 ml.) was treated with the per-acid (3·0 g.) during 20 min. and stirred for a further 1·5 hr. A crystalline precipitate (2·2 g.) was filtered off, and the filtrate neutralised and evaporated to small volume. The aqueous solution was extracted with ether (from which 0·9 g. of the amine was recovered) and, after acidification with concentrated hydrochloric acid, with butan-1-ol. The butanol extract was neutralised with ammonia and evaporated to dryness. From an aqueous solution of the residue, 0·5 g. of a substance, m. p. 160—163°, crystallised. Recrystallisation of the combined precipitates from 70% aqueous acetone gave plates, m. p. 167—169°. The product was acidic and contained phosphate ion, but was not precipitated on addition of alkali (the amine is not soluble in water). Analysis indicated that the compound was the *oxide phosphate* (Found: P, 10·8, 10·7; N, 4·9. $C_{12}H_{13}ON,H_3PO_4$ requires P, 10·9; N, 4·9%). The oxide (0·5 g.) was kept in concentrated hydrochloric acid with stannous chloride (0·5 g.) overnight at room temperature and then made alkaline and extracted with ether. Evaporation of the extract and crystallisation of the residue from aqueous ethanol yielded *NN*-dimethyl-2-naphthylamine, m. p. and mixed m. p. 44—45° (Found: C, 83·9; H, 8·1; N, 8·05. Calc. for $C_{12}H_{13}N$: C, 84·2; H, 7·7; N, 8·2%).

Oxidation of Aniline by Permonophosphoric Acid.—Permonophosphoric acid (10 g. in acetonitrile) was added during 30 min. with cooling and stirring to aniline (15 g.) in acetone (200 ml.). After a further 1·5 hr. the solution was neutralised with 2N-sodium hydroxide and evaporated to small volume under reduced pressure. After dilution with water and adjustment to pH 5·0, the solution was extracted with ether, then with butan-1-ol and again with this solvent at

[14] Titley, *J.*, 1928, 2571.
[15] Billman, Radike, and Munday, *J. Amer. Chem. Soc.*, 1942, **64**, 2977.

pH 2·0. The ether extracts contained *p*-aminophenol and evaporation of the butanol extracts and benzoylation of the residue in pyridine with benzoyl chloride yielded *p*-benzamidophenyl benzoate (10 mg.), m. p. and mixed m. p. 230—232°. Paper chromatography showed that the butanol extracts contained no *p*-aminophenyl phosphate. The ester was identified in the aqueous layer by comparison on paper chromatography with a known specimen [R_F 0·35 in solvent system (*a*)]. The spot gave a yellow colour after diazotisation and coupling with hexylresorcinol. Two other spots with the same colour reaction and with R_F respectively 0·56 and 0·16 were present but were not identified. *p*-Aminophenyl phosphate was not isolated.

Oxidation of Aniline by Peracetic Acid in the Presence of Phosphoric Acid.—40% Peracetic acid (38 ml.) was added during 45 min. with cooling to aniline (18·6 g.) and phosphoric acid (39·2 g.) in acetone (350 ml.). Water (50 ml.) was added and the mixture neutralised with 2N-sodium hydroxide and evaporated to small volume. More water (250 ml.) was added and the solution extracted with ether. Paper chromatography showed the extract to contain aniline and *p*-aminophenol. Extraction of the aqueous layer, adjusted to pH 5·0 by 2N-hydrochloric acid, with butan-1-ol removed more *p*-aminophenol. During this last extraction a solid (2·1 g.) crystallised from the aqueous layer, and was collected. The solution, acidified to pH 2·0, yielded no amino-compounds on extraction with butanol. It was neutralised and evaporated to dryness. The residue was extracted with hot methanol, and the extract evaporated to dryness. The residue was dissolved in water and the solution adjusted to pH 5·0 and cooled, to yield needles (1·1 g.). These, and the material obtained as above, were recrystallised from 10% ethanol to yield, in both cases, needles, m. p. 191—192° with no mutual depression of m. p. Paper chromatography in solvent system (*a*) showed both to have the same R_F (0·35) as the *p*-aminophenyl phosphate obtained as below. The ester was isolated as *sodium* p-*aminophenyl hydrogen phosphate* (Found: P, 14·3; N, 6·3; Na, 11·5. $C_6H_7O_4NPNa$ requires P, 14·7; N, 6·6; Na, 10·9%). Hydrolysis of the ester with 5N-hydrochloric acid at 100° for 30 min. and benzoylation of the product yielded *p*-benzamidophenyl benzoate, m. p. and mixed m. p. 230—232° (Found: N, 4·6. Calc. for $C_{20}H_{15}O_3N$: N, 4·4%). *p*-Aminophenyl phosphate gave colour tests like those of 2-amino-1-naphthyl phosphate.

Disodium p-*Aminophenyl Phosphate formed by the Reduction of the Nitro-compound.*—Disodium *p*-nitrophenyl phosphate (0·5 g.) in 50% aqueous ethanol (50 ml.) was reduced with hydrogen and Adams catalyst (0·1 g.) at room temperature and pressure. After filtration, the solution was evaporated to dryness and the residue crystallised from aqueous ethanol (approx. 50%), to yield *disodium* p-*aminophenyl phosphate* as needles (0·15 g., 30%) (Found: P, 13·1; N, 5·8. $C_6H_6O_4NPNa_2$ requires P, 13·3; N, 6·0%).

Oxidation of Anthranilic Acid.—Permonophosphoric acid (10 g., in acetonitrile) was added during 30 min. to anthranilic acid (14 g.) in acetone (50 ml.) and water (50 ml.). After 4 hours' stirring and storage overnight the solution was neutralised and evaporated to small volume. The solution was adjusted to pH 4·0 and continuously extracted with ether for 24 hr. Yellow prisms crystallised from the ether extract and, after recrystallisation from alcohol, had m. p. 245—246° (1·0 g.). Paper chromatography of the ether extracts in solvent system (*b*) showed the presence of anthranilic acid (R_F 0·95, yellow colour after diazotisation and coupling with hexylresorcinol) and 5-hydroxyanthranilic acid (R_F 0·6, red colour with above reagents). No 3-hydroxyanthranilic acid appeared to be present (the authentic compound had R_F 0·9 and formed a pale yellow colour with the above reagents). Acidification of the aqueous layer to pH 1·0, followed by extraction with ether, gave more (0·25 g.) of the compound, m. p. 245°, which was acidic, did not diazotise, couple with hexylresorcinol, or give a colour with diazotised sulphanilic acid. The compound gave no m. p. depression with azoxybenzene-2 : 2′-dicarboxylic acid [16] (Found: C, 58·8; H, 3·5; N, 10·15. Calc. for $C_{14}H_{10}O_5N_2$: C, 58·7; H, 3·5; N, 9·8%). Examination of the aqueous fraction by paper chromatography revealed no diazotisable compounds.

Attempted Oxidation of 2-Naphthylamine with Alkaline Perdiphosphate.—2-Naphthylamine (0·5 g.) was treated with perdiphosphate (1 equiv.) and the mixture examined by paper chromatography in solvent system (*a*). No 2-amino-1-naphthyl phosphate was formed with either potassium or ammonium perdiphosphate under the following conditions: (1) neutral aqueous solution, at room temperature up to 10 days; (2) aqueous alkaline solutions at room temperature, or at 100° for 4 hr.; (3) alkaline 50% acetone for up to 10 days at room temperature. Reaction in the presence of added phosphoric acid gave no phosphoric esters unless acetone was

[16] Heller, *Ber.*, 1908, **41**, 2690.

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present. However, on a preparative scale (6·3 g. of amine) the use of this method at room temperature gave only a few mg. of phosphoric ester. Experiments with aniline gave similar results.

Paper Chromatography of Acetone and Acetonitrile Solutions of Permonophosphoric Acid.—Solutions (10%) of permonophosphoric acid in acetonitrile or acetone were kept for 2 hr. at room temperature and samples of each applied to chromatography paper. The spots were neutralised with ammonia vapour, and the chromatograms developed in solvent system (*a*) for 16 hr. Phosphates were detected by Hanes and Isherwood's method [13] (ascorbic acid as the reducing agent [17]). Oxidising substances were detected by a 5% aqueous potassium iodide spray. Permonophosphoric acid had R_P 0·25 and phosphoric acid R_P 0·35. If the acetone solution was kept for 48 hr. at room temperature only the oxidising spots at R_P 0·5 and 0·85 and phosphoric acid were detectable.

The effects of solvents on the oxidation of 2-naphthylamine were studied by dissolving the amine (0·5 g.) in the solvent (15 ml.), and adding 0·3 g. of permonophosphoric acid. The mixtures were examined by paper chromatography.

Analyses were by Mr. F. H. Oliver, of the Microanalytical Laboratory, Imperial College of Science and Technology, and Mr. P. Baker, of Wellcome Research Laboratories. This investigation has been supported by grants to the Chester Beatty Research Institute (Institute of Cancer Research: Royal Cancer Hospital) from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

The Chester Beatty Research Institute,
The Institute of Cancer Research: Royal Cancer Hospital,
Fulham Road, London, S.W.3. [*Received, June 12th,* 1957.]

[17] Rouser and Neuman, *Fed. Proc.*, 1952, **11**, 278.

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948. *Reactions of Esters of Phosphorothioic Acid. Part I. A Comparison of the Hydrolyses of Triethyl Phosphorotrithiolate and Triethyl Phosphate.*

By E. M. Thain.

Measurements have been made of the rates of hydrolysis of triethyl phosphorotrithiolate and phosphate under acidic, neutral, and alkaline conditions. It has been shown, by isolation of ethanethiol, that such hydrolysis of the former compound involves fission of the P–S bond. Towards alkaline hydrolysis the thiolester is 1500 times more reactive than the oxygen ester, mainly owing to a difference in the Arrhenius frequency factors. In acid and in neutral solution the rates of hydrolysis for both esters are similar, and much smaller than in alkali. The theoretical implications of these results are discussed.

Whilst the rates of hydrolysis and positions of bond-fission have been determined for some triesters of orthophosphoric acid, such as trimethyl [1,2,3] and triphenyl phosphate,[2,3] little work has been done on esters derived from thiols and orthophosphoric acid, *e.g.*, triethyl phosphorotrithiolate, $(EtS)_3PO$. The aim of this study has been to compare the hydrolysis of triethyl phosphorotrithiolate with that of triethyl phosphate, and to determine the position of bond-fission for the thiolester.

In the hydrolysis of trimethyl phosphate both possible positions of bond-fission have been observed; [2,3] thus in alkaline hydrolysis the P–O bond is broken, whilst in neutral and acid hydrolysis C–O fission occurs. Carbon–oxygen bond-fission also occurs in trialkyl phosphates when these esters act as alkylating agents, *e.g.*, for phenols,[4] alcohols,[5] and

[1] Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611.
[2] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.
[3] Vernon, *Chem. Soc. Symposium*, Cambridge, 1957.
[4] Dutton and Noller, *J. Amer. Chem. Soc.*, 1933, **55**, 424.
[5] Toy, *ibid.*, 1944, **66**, 499.

amines.[6] The two possible positions of bond-fission would, in the hydrolysis of triethyl phosphorotrithiolate, yield different products: P–S fission would give ethanethiol and diethyl phosphorodithiolate; and C–S fission would give ethanol and diethyl phosphorodithiolothionate, $(EtS)_2PS{\cdot}OH$. The latter compound would be expected to hydrolyse further, giving hydrogen sulphide and diethyl phosphorodithiolate.[7]

Triethyl phosphorotrithiolate had been prepared previously,[8, 9, 10] but no details of its acid- or alkali-catalysed hydrolysis were given. However, Hudson and Keay [11] have found that with di*iso*propyl methylphosphonodithiolate P–S fission occurs in both types of hydrolysis. In the present work an attempt to estimate ethanethiol, at points throughout the hydrolysis, by the iodometric method [12] used by Hudson and Keay, was unsuccessful; poor end-points, possibly owing to reaction between iodine and unchanged thiolester, were observed. The products of the reaction, from the nature of which the position of bond fission could be inferred, were therefore investigated by direct isolation.

Because of the insolubility of triethyl phosphorotrithiolate in water, alkali-catalysed hydrolysis of this ester and of triethyl phosphate was studied in 50% aqueous dioxan. Second-order rate-coefficients were constant in any one run; collected values are shown in Table 1.

Reaction of the thiolester is clearly of the second order, and therefore presumably bimolecular, since the rate-coefficient varies only slightly with concentration of hydroxide

TABLE 1. *Second-order rate-coefficients for the alkali-catalysed hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in 50% aqueous dioxan.*

Temp.	[KOH] (N)	[Ester] (M)	$10k_2$ (l. mole^{-1} min.$^{-1}$)	Temp.	[KOH] (N)	[Ester] (M)	$10k_2$ (l. mole^{-1} min.$^{-1}$)
		$(EtS)_3PO$				$(EtO)_3PO$	
0°	0·0615	0·0227	0·834	40·9°	0·0546	0·0326	0·0177
0	0·0612	0·0246	0·858	82·0	0·0703	0·0388	0·277
25	0·0644	0·0193	7·52				
25	0·1172	0·0233	7·18				
25	0·0748	0·0221	7·51				

ion, and also because the solvolytic reaction is very slow at this temperature. The small decrease observed in k_2 as the concentration of hydroxide ion is increased would be expected [13] for a reaction between the hydroxide ion and a neutral molecule. It is not possible to decide from the kinetic results whether the hydrolysis involves a one-stage synchronous displacement, or a rapid reversible formation of a quinquecovalent intermediate. However, isotope studies [14] on the bimolecular solvolysis of diethyl phosphorochloridate show no evidence for the reversible formation of an intermediate. Since the hydrolysis proceeds by fission of the P–S bond it is suggested that the most likely formulation for the alkaline hydrolysis of the thiolester is:

This mechanism is analogous to that proposed for the alkaline hydrolysis of trimethyl phosphate in water.[2]

[6] Thomas, Billman, and Davis, *J. Amer. Chem. Soc.*, 1946, **68**, 895.
[7] Pischchimuka, *J. Chim. Ukraine*, 1925, **1**, 87.
[8] *Idem*, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1406.
[9] Lippert and Reid, *J. Amer. Chem. Soc.*, 1938, **60**, 2370.
[10] Chapman and Saunders, *J.*, 1948, 1010.
[11] Hudson and Keay, *J.*, 1956, 3269.
[12] Böhme and Schran, *Chem. Ber.*, 1949, **82**, 456.
[13] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 347.
[14] Dostrovsky and Halmann, *J.*, 1956, 1004.

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For comparison the rate of alkaline hydrolysis of triethyl phosphate was measured in the same solvent. Although it was not shown rigorously that this hydrolysis is of the second order, it is considered to be so (*a*) because constant second-order coefficients are found in any one run, (*b*) because the neutral solvolytic rate is slow, and (*c*) from analogy with the alkaline hydrolysis of trimethyl phosphate.[2] The oxygen-ester was found to be less reactive than the thiolester; thus the calculated rate at 25° was 1500 times slower. The Arrhenius parameters, which are given in Table 2, show that this difference is due mainly to the lower Arrhenius frequency factor of the oxygen-ester. The activation energies are comparable, though even here the values indicate that the thiolester is the more reactive. It is usually considered that the frequency factor is, in transition-state theory, a measure of the entropy of activation. Therefore the lower entropy of activation of the oxygen-ester suggests that in this compound a more rigid transition state is formed.

TABLE 2. *The Arrhenius parameters for the alkaline hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in 50% aqueous dioxan.*

	E (kcal. mole^{-1})	log PZ (l. mole^{-1} min.$^{-1}$)
$(EtS)_3PO$	14·1	10·2
$(EtO)_3PO$	14·9	7·6

Hudson and Keay [11] observed that in the alkaline hydrolyses of di*iso*propyl methylphosphonodithiolate and methylphosphonate the thiolester had, first, a lower activation energy (11·4 compared with 14·9 kcal. mole^{-1}) and, secondly, a higher Arrhenius frequency factor (log PZ 7·3 compared with 5·4). These workers attributed the increase in the frequency factor to the greater covalent radius of sulphur than of oxygen. Thus the *iso*propyl group was removed further from the reaction site in the thiolester, and caused less strain in the formation of the transition state. Similar considerations also apply to triethyl phosphorotrithiolate. Schaefgen,[15] and Rylander and Tarbell [16] pointed out an additional factor influencing the entropy of activation in the alkaline hydrolysis of ethyl thiolacetate and of ethyl acetate, suggesting that the oxygen-ester is hydrated, by hydrogen bonding, to a greater extent than is the thiolester, and that the consequent steric hindrance would cause the oxygen-ester to have a lower entropy of activation. It seems possible that this argument is also relevant to the phosphoric esters, for it has been noticed that, whilst triethyl phosphate is completely miscible with water, triethyl phosphorotrithiolate is only slightly soluble; rough experiments suggest a figure less than 0·2% at 25°. This difference in solubility is attributed to hydration, through hydrogen bonding, of the oxygen-ester.

Acid-catalysed hydrolysis of these two esters was studied in 60% aqueous dioxan, because the Hammett acidity function, H_0, has been measured in this solvent.[17] The medium was made up from 60% aqueous dioxan and 60% perchloric acid, further dioxan being added so as to keep the water : dioxan ratio constant. The first-order rate-coefficients for the neutral solvolysis, and for the acid-catalysed hydrolysis, of the two esters are shown in Table 3. The hydrolysis of the thiolester, which proceeds by fission of the P–S bond, shows acid-catalysis clearly, and over a limited range the rate is proportional to stoicheiometric acidity, and not to the H_0 function. There is, on the contrary, a tendency at higher acidities for the increase in rate to be less that that required by a linear relation. On the basis of the Hammett–Zucker hypothesis [18] this means that the rate-determining step involves a water molecule. Consequently, the mechanism of this hydrolysis is considered to be nucleophilic attack by water on the phosphorus atom of the protonated ester, $(EtS)_3P{=}\overset{+}{O}H$. The rate of the reaction was not altered on the addition of sodium perchlorate, although a small decrease [13] might have been forecast for this type

[15] Schaefgen, *J. Amer. Chem. Soc.*, 1948, **70**, 1308.
[16] Rylander and Tarbell, *ibid.*, 1950, **72**, 3021.
[17] Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.
[18] L. P. Hammett, "Physical Organic Chemistry," McGraw Hill Book Co., New York, 1940, p. 276.

of reaction. The cause of the non-linearity of the rate with stoicheiometric acidity at the higher acid concentrations is not known. It is of interest that this phenomenon has been observed in the acid-catalysed hydrolysis of other phosphoric esters.[3] It seems unlikely that it is due to approach towards complete protonation of the ester, and it has been suggested [3] that it is due to a decrease in the activity of water, in mixed-solvent systems at high acid concentrations.

TABLE 3. *First-order rate-coefficients for the neutral solvolysis and the acid-catalysed hydrolysis of* $(EtS)_3PO$ *and* $(EtO)_3PO$ *in 60% aqueous dioxan at 82°.*

$[HClO_4]$ (N)	$[NaClO_4]$ (N)	10^5k_1 (min.$^{-1}$)	$[HClO_4]$ (N)	$[NaClO_4]$ (N)	10^5k_1 (min.$^{-1}$)
$(EtS)_3PO$			$(EtO)_3PO$		
0	0	0·25	0	0	0·53
0	0·515	1·16	0	0·27	0·60
0·049	0	2·0	0·27	0	2·52
0·27	0	7·13	Solvolysis in water at 82°		9·50
0·27	0·26	7·15			
0·385	0	8·16			
0·938	0	15·1			
1·436	0	21·9			

An acid-catalysed hydrolysis was found also for triethyl phosphate in 60% aqueous dioxan; and, in contrast to the case of alkaline hydrolysis, the rate was not significantly different from that of the thiolester. However, no valid comparison can be made here, because the position of bond-fission is not known: analogy with trimethyl phosphate [2] suggests C–O fission. Presumably the reactive conjugate acid of the thiolester has a proton attached to the phosphoryl-oxygen atom, nucleophilic attack on phosphorus being thereby made easier. This mechanism leads to P–S fission. In the oxygen-ester, on the other hand, C–O fission being assumed, the reactive conjugate acid must contain a proton attached to an ether-oxygen atom. The near-identity of the rates of the two processes is clearly fortuitous.

It is of interest that, whereas triethyl phosphate shows acid-catalysed hydrolysis in 60% aqueous dioxan, in water the hydrolysis of trimethyl phosphate is independent of acid concentration.[2] Presumably this is because the neutral solvolysis rate is strongly solvent-dependent, and in water the rate is sufficiently great to mask acid-catalysis. Thus, at 82°, for triethyl phosphate, neutral solvolysis in water is four times faster than acid-catalysed (0·27N-$HClO_4$) solvolysis in 60% aqueous dioxan, and 20 times faster than neutral solvolysis in this solvent. Consistently, the neutral rates of both esters, in 60% aqueous dioxan, are accelerated by addition of sodium perchlorate; the increase for the oxygen-ester is, however, smaller than might be expected.

The bond energies, quoted by Hudson and Keay [11] (P–S, 45—50 kcal. mole^{-1}; P–O, 95—100 kcal. mole^{-1}), suggest that the P–S would be more readily broken than the P–O bond. Although this is in accordance with the results now presented for the alkaline hydrolysis, yet if bond energies were of major importance in determining the relative rates of hydrolysis a greater difference in the activation energies might be expected for these two esters.

EXPERIMENTAL

Triethyl Phosphorotrithiolate.—Phosphoryl chloride (13 ml.; freshly distilled) was added dropwise with stirring to an ice-cold solution of ethanethiol (37·6 g.) and triethylamine (61·2 g.) in dry ether (200 ml.). On completion of the addition, the mixture was boiled under reflux for 2 hr. Triethylamine hydrochloride was filtered off and washed with ether. The combined ethereal filtrates were evaporated under reduced pressure, and the residual oil was distilled, yielding the ester (81%), b. p. 85—89°/0·2 mm., n_D^{25} 1·5764. This material contained an

impurity which was hydrolysed, in alkali, much faster than the pure thiolester and was shown not to be diethyl phosphorodithiolochloridate.

The crude ester (27 g.) was dissolved in a mixture of dioxan (140 ml.) and water (60 ml.) containing potassium hydroxide (0·1 g.). After storage overnight, dioxan and water were removed under reduced pressure, and the residue was dissolved in ether (50 ml.), washed with water, and dried ($CaSO_4$). After removal of ether, distillation afforded the pure ester, b. p. 89°/0·2 mm., n_D^{25} 1·5676 (Found: C, 31·3; H, 6·5; S, 41·9; P, 13·7. Calc. for $C_6H_{15}OS_3P$: C, 31·3; H, 6·5; S, 41·7; P, 13·5%).

Triethyl phosphate was prepared from sodium ethoxide and phosphoryl chloride;[19] the fraction with the following properties was collected: b. p. 97—98°/15 mm., n_D^{25} 1·4036.

Kinetic Experiments.—Purified dioxan[20] was used; the term "x% aqueous dioxan" refers to a solvent prepared by mixing x volumes of purified dioxan with $(100 - x)$ volumes of distilled water.

Alkaline Hydrolysis.—Hydrolysis of the thiolester in 50% aqueous dioxan, in the presence of potassium hydroxide, was followed by acid–base titration. Since ethanethiol is relatively acidic, the stoicheiometric equation for the hydrolysis is:

$$(EtS)_3PO + 2OH^- \longrightarrow (EtS)_2PO{\cdot}O^- + EtS^- + H_2O$$

and the appropriate integrated rate equation is:

$$k_2 = \frac{2{\cdot}303}{t(b - 2a)} \cdot \log_{10} \frac{a(b - 2x)}{b(a - x)}$$

where a is the initial molarity of the thiolester, b is the initial molarity of the hydroxide ion, and x is the amount of the thiolester, expressed as a molarity, hydrolysed after time, t.

For hydrolysis of triethyl phosphate, the rate equation is:

$$k_2 = \frac{2{\cdot}303}{t(b - a)} \log_{10} \frac{a(b - x)}{b(a - x)}$$

corresponding to the stoicheiometric equation:

$$(EtO)_3PO + OH^- \longrightarrow (EtO)_2PO{\cdot}O^- + EtOH$$

About 1·5 g. of the ester were accurately weighed in a 250 ml. graduated flask which was then brought to thermal equilibrium in a thermostat. To it was added a solution of potassium hydroxide (*ca.* 0·05N) in 50% aqueous dioxan, which had been brought to the same temperature. Aliquot parts (10 ml.) were withdrawn at intervals and diluted with water, and excess of alkali was titrated against 0·02N-hydrochloric acid (phenolphthalein). It was shown that ethanethiol did not interfere with this titration. Calculated and experimental infinity values agreed well.

The following results for the hydrolysis of 0·01934M-triethyl phosphorotrithiolate in 50% aqueous dioxan containing potassium hydroxide (0·0644N) at 25° are typical:

Time (min.)	0	3·4	10·3	14·2	18·9	24·2	29·5	38·5	58·4	∞
Titre (0·02N-HCl)	32·22	30·80	28·70	27·88	27·18	26·49	25·80	25·07	24·24	22·55
$10k_2$ (l. mole^{-1} min.$^{-1}$)		7·59	7·77	7·61	7·43	7·37	7·67	7·66	7·07	

The initial reading was taken 2 min. after mixing.

Acid-catalysed Hydrolysis.—Since it was noticed that in acid and neutral solutions the rates of hydrolysis were increased by oxygen, all the kinetic runs under these conditions were done under oxygen-free nitrogen. Standard solutions of the esters were prepared in 60% aqueous dioxan–perchloric acid mixtures, which had previously been freed from oxygen by boiling under reflux in a stream of oxygen-free nitrogen. Equal volumes of the ester solution were dispensed from an automatic pipette into "Monax" tubes, the air was displaced by

[19] Evans, Davies, and Jones, *J.*, 1930, 1310.
[20] A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 175.

oxygen-free nitrogen, and the tubes were sealed. After appropriate intervals in the thermostat, tubes were removed, washed with distilled water, and smashed under distilled water. The perchloric acid was neutralised by the addition, from an automatic pipette, of potassium hydroxide solution of such a strength as to be almost exactly equivalent to the initial concentration of perchloric acid. Excess of acid, produced by hydrolysis, was then estimated by titration with *ca.* 0·02N-potassium hydroxide to phenolphthalein. Infinity values were calculated from the weight of the ester taken. The following data for the hydrolysis, at 82°, of triethyl phosphorotrithiolate (1·0622 g./100 ml.) in 60% aqueous dioxan containing perchloric acid (0·938N) are typical. The sealed tubes contained 5·26 ml. of the acid solution; after they had been broken under distilled water, 0·875N-potassium hydroxide (5·52 ml.) was added, and the residual acid was titrated against 0·0182N-potassium hydroxide.

Time (hr.)	0	18·42	25·17	42·42	49·92	66·42	73·92	∞
Titre (ml.)	8·45	10·40	11·18	12·30	13·40	14·70	15·35	21·80
10^4k_1 (min.$^{-1}$)		1·43	1·51	1·34	1·55	1·59	1·65	

Products of Hydrolysis of Triethyl Phosphorotrithiolate.—The ester (0·11 g.) was dissolved in oxygen-free 60% aqueous dioxan (5 ml.), containing perchloric acid (1·2N), sealed in a " Monax " tube under oxygen-free nitrogen, and heated at 82° for 4 days. After being cooled to 0° the tube was opened, and the contents transferred to a small two-necked flask fitted with a reflux condenser, the top of which was connected to a trap containing 5% mercuric cyanide solution (3 ml.). A slow stream of nitrogen was passed through the acid solution, which was then heated to the b. p. The mercuric salt of ethanethiol was precipitated in the trap in nearly quantitative yield; the solid was completely soluble in hot ethanol from which it readily crystallised (m. p. and mixed m. p. 78°). No mercuric sulphide was formed, even on prolonged boiling. A similar result was obtained on alkaline hydrolysis of the ester (0·11 g.), at 25° for 24 hr., in 50% aqueous dioxan (5 ml.) containing potassium hydroxide (0·1N). Since the solvolysis of the thiolester in 60% aqueous dioxan is slow, a tube from a kinetic run, which had been kept at 82° for five weeks, was treated with acid, as above. The yield of the mercuric salt of ethanethiol was low (10%), but corresponded fairly well with the extent of hydrolysis. No mercuric sulphide was produced.

cyclo*Hexylamine Diethyl Phosphorodithiolate.*—Triethyl phosphorotrithiolate (2 g.) was added to 60% aqueous dioxan (40 ml.) containing sodium hydroxide (1 g.). The emulsion was shaken for 12 hr. at room temperature, after which the solution was clear. The water and dioxan were removed by distillation under reduced pressure, the solid residue was dissolved in water (20 ml.), and unchanged ester removed by washing the aqueous solution with ether (10 ml.). Sodium ions were removed on a column of ion-exchange resin, IR-120, in its hydrogen form. The acid eluate was neutralised with *cyclo*hexylamine, and reduced to small volume. The cyclo*hexylamine salt* crystallised readily as fine needles (1·6 g.), m. p. 182—183°, unchanged on recrystallisation from water (Found: C, 41·8; H, 8·5; N, 4·9; P, 10·9; S, 22·2. $C_{10}H_{24}O_2NS_2P$ requires C, 42·1; H, 8·4; N, 4·9; P, 10·9; S, 22·4%).

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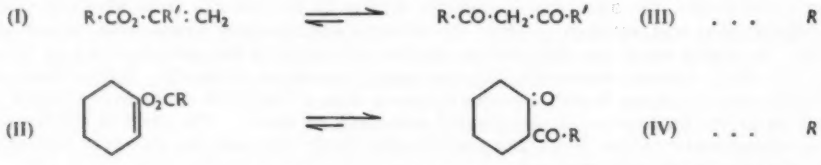
949. *Studies in Pyrolysis. Part XII.*‡ *Reversible Thermal Rearrangement as a Competitive Route in the Pyrolysis of Enol Carboxylates.*

By R. J. P. Allan, J. McGee, and P. D. Ritchie.

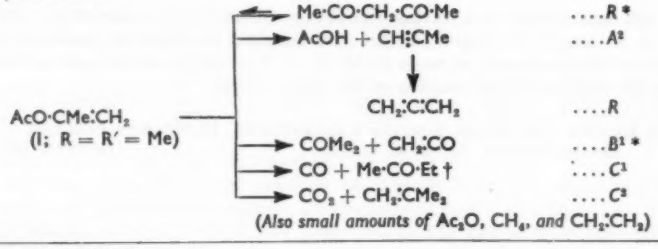
The previously described formation of β-diketones by thermal rearrangement [1] of enol carboxylates (other than vinyl esters) is shown to be reversible. In the vapour phase at *ca.* 500° the equilibrium strongly favours the β-diketone. The enol carboxylates studied (*iso*propenyl acetate, *cyclo*hex-1-enyl acetate, and *cyclo*hex-1-enyl benzoate) undergo, in addition to the above change, a series of minor competitive scissions, including decarboxylation to an alkene. By-products are discussed.

Various enol carboxylates (*e.g.*, I; R = Me, R′ = Me or Ph: II; R = Me) isomerise thermally [1] in the vapour phase at *ca.* 500°, giving good yields of the corresponding β-diketones (III) and (IV) respectively. This is believed [1] to involve a four-centre transition-state, a concept possibly also applicable to a number of other related thermal rearrangements.[2] Work on three enol carboxylates (I; R = R′ = Me), (II; R = Me or Ph) and two of the corresponding β-diketones (III; R = R′ = Me: IV; R = Ph) has now revealed the unexpected fact that the rearrangement *R* is reversible, with the equilibrium point lying far over to the β-diketone side, thus:



This is clearly demonstrated by pyrolysis of the pure β-diketones (III) and (IV); in each case, the pyrolysate contains *inter alia* a small amount of the corresponding enol carboxylate.

Young *et al.*[1] recorded no by-products from these pyrolyses. It was, however, shown later by Allan, Forman, and Ritchie [3] that vinyl carboxylates [*i.e.*, those enol carboxylates (I) in which R′ = H] break down under similar conditions by a complex series of competitive scissions; we have demonstrated that this is true of enol carboxylates in general. The best overall interpretation of the results is offered by the following schemes, in which * indicates a major route and † a product identified in the pyrolysate from the ester only, not from the β-diketone:

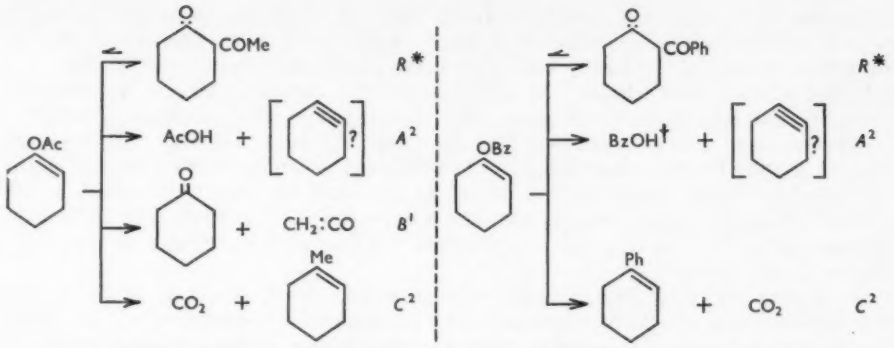


‡ Part XI, *J.*, 1957, 2564.

[1] Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635; Boese and Young, U.S.P. 2,395,800/1946, B.P. 615,523/1949.

[2] See, *e.g.*, Chapman, *J.*, 1927, 1743; Schönberg *et al.*, *Ber.*, 1930, **63**, 178; *Annalen*, 1930, **483**, 107; Wiberg *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 2665; 1955, **77**, 2205, 2774; White, *ibid.*, 1955, **77**, 6011, 6014; Al-Kazami, Tarbell, and Plant, *ibid.*, 1955, **77**, 2479.

[3] Allan, Forman, and Ritchie, *J.*, 1955, 2717.



(*Also* CO, *and small amounts of* Ac_2O, $COMe_2$, $CH_2{:}CH_2$, *and cyclohexene*)

(*Also* CO, $CH_2{:}CH_2$, *benzene, and cyclohexanone*

Discussion

Rearrangement (*R*).—In all cases studied, the β-diketone is the major product from pyrolysis of the ester. Further, in agreement with this, the pure diketone is found to be more thermostable than its parent ester: its pyrolysis under the same conditions gives only a minor overall breakdown, though the formation of a small amount of enol carboxylate is proved by a combination of chemical and spectrometric methods.

Allan *et al.*[3] showed that the competitive scissions undergone by vinyl esters include a decarbonylation occurring in two stages, (i) a primary rearrangement (*R*), similar to that described above, but yielding a labile β-keto-aldehyde instead of a stable β-diketone, followed by (ii) a decarbonylation (C^1) of the rearrangement product. (This C^1 reaction is predictable for aldehydes, but not in general for ketones.) Here, also, *R* may possibly by an equilibrium process, the two-stage sequence being formulated thus:

$$R{\cdot}CO_2{\cdot}CH{:}CH_2 \underset{I}{\overset{R}{\rightleftharpoons}} [R{\cdot}CO{\cdot}CH_2{\cdot}CHO] \xrightarrow{C^1} CO + R{\cdot}CO{\cdot}Me$$

However, the instability of the intermediate will here displace the equilibrium still further away from the ester, virtually precluding detection of the latter in a separate pyrolysis of the pure β-keto-aldehyde. It has, in fact, already been shown [3] that benzoylacetaldehyde (III; R = Ph, R′ = H) is almost completely decarbonylated at *ca.* 550°, and, although a little survives at *ca.* 400°, re-examination of the infrared spectrum of the pyrolysate has shown no trace of the corresponding enol carboxylate, vinyl benzoate.

Bailey *et al.*[4] have shown that carbonised deposits (presumed to be acidic) formed during pyrolysis of an ester can catalytically induce rearrangement of certain of the primary products, notably olefins. No carbonisation was reported by Young *et al.*,[1] but in the present work it was found that carbonisation, though slight, was unavoidable at the high temperatures necessary for scission, so that carbonised deposits may possibly affect catalytically the competitive scissions noted. Certainly, the rearrangement (*R*) of enol carboxylates can be caused not only thermally, but also catalytically (*e.g.*, by bases [5] or boron trifluoride,[1] though in the special case of vinyl esters the latter causes violent polymerisation, even at −40°, rather than detectable rearrangement [6]).

A^2 Scission.—It is not certain whether methylacetylene and allene are both formed directly (*i.e.*, competitively) from *iso*propenyl acetate, or whether one is the precursor of the other. Hurd *et al.*[7] showed that an alk-1-yne is partially isomerised to an alka-1 : 2-diene at *ca.* 500°, but that the reverse change does not appear to occur thermally (though it can be

[4] Bailey *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 73, 75, 357.
[5] Claisen and Haase, *Ber.*, 1903, **36**, 3674; Dieckmann and Stein, *Ber.*, 1904, **37**, 3370.
[6] Allan, Ph.D. Thesis, Glasgow University, 1956, p. 51.
[7] Meinert and Hurd, *J. Amer. Chem. Soc.*, 1930, **52**, 4549; Hurd and Meinert, *ibid.*, 1931, **53**, 292; Hurd and Christ, *ibid.*, 1937, **59**, 2161.

induced catalytically). This, coupled with the fact that an alkyne is formed from vinyl [3] as well as from *iso*propenyl acetate, by a minor scission, suggests that methylacetylene is a primary product of the latter, with subsequent partial isomerisation (*R*) to allene, as indicated in the above scheme. Nevertheless, another possibility cannot be excluded. Formally, the acetoxy-group of *iso*propenyl acetate may, on elimination, abstract a β-hydrogen atom from either of two dissimilar sites; the work of Bailey *et al.*[4] suggests that one of these (the α-methyl group) should be favoured when the reaction vessel is clean, yielding allene directly in the early stages of the pyrolysis, by what is essentially an A^1 rather than an A^2 scission, whereas the other site (the methylene group) should become increasingly favoured as carbonisation develops, yielding methylacetylene by direct A^2 scission in the later stages.

By analogy with these results, it seems that the acid formed on pyrolysis of the *cyclo*hex-1-enyl carboxylates should be accompanied by an acetylene (*cyclo*hexyne) and an allene (*cyclo*hexa-1 : 2-diene). As expected, there was no evidence for these transient entities (*cyclo*hexyne is [8] incapable of stable existence); but neither was there evidence for any of their probable secondary reactions—for example, rearrangement to *cyclo*hexa-1 : 3-diene, trimerisation to dodecahydrotriphenylene, or disproportionation to benzene plus *cyclo*hexene. (Benzene is obtained from the benzoate *only*, and *cyclo*hexene from the acetate *only*.) This A^2 reaction is therefore less well established than that of *iso*propenyl acetate, though it is difficult to account for the observed carboxylic acid on any other basis.

B^1 *Scission.*—This reaction, though structurally precluded for an enol benzoate, competes quite strongly in the pyrolysis of the two acetates (cf. the corresponding results [3] for vinyl benzoate and acetate). Both the acetates also yield a trace of acetic anhydride, probably formed by interaction of acetic acid (route A^2) and keten (route B^1). At least one ester, benzyl benzoate, yields [9] an acid anhydride and an ether, by disproportionation (*D*); but the *D* reaction is an unlikely origin for the anhydride now observed, since *cyclo*hex-1-enyl benzoate yields no benzoic anhydride, and vinyl carboxylates [10] no divinyl ether.

C^1 *Scission.*—Formation of a trace of ethyl methyl ketone from *iso*propenyl acetate is unexpected. No simple rearrangement of the type discussed could lead to a readily decarbonylated β-keto-aldehydic precursor such as Me·CO·CHMe·CHO or Et·CO·CH_2·CHO (the latter is claimed [3] as the direct precursor of the ethyl methyl ketone formed on pyrolysis of ethylene dipropionate [11]). Conceivably, the ketone might arise by direct semidecarbonylation of acetylacetone, but this is unlikely since it was not detected when the equilibrium system was approached from the β-diketone side by pyrolysis of pure acetylacetone, a negative result which agrees with an earlier study of this pyrolysis.[12] The explanation may lie in the following tentative sequence of high-temperature free-radical reactions, in which the *iso*propenyloxy-radical (·O·CMe:CH_2), formed by the initial scission, reacts preferentially (at least in part) in its alternative canonical form, the acetonyl radical (O:CMe·CH_2·), thus:

(i) $Me{\cdot}CO{\cdot}O{\cdot}CMe{:}CH_2 \longrightarrow Me{\cdot}CO{\cdot} + {\cdot}O{\cdot}CMe{:}CH_2$

(ii) $Me{\cdot}CO{\cdot} \longrightarrow Me{\cdot} + CO$

(iii) ${\cdot}O{\cdot}CMe{:}CH_2 \longleftrightarrow O{:}CMe{\cdot}CH_2{\cdot}$

(iv) $O{:}CMe{\cdot}CH_2{\cdot} + Me{\cdot} \longrightarrow Me{\cdot}CO{\cdot}CH_2{\cdot}Me$

However, although this type of free-radical sequence seems equally applicable to *cyclo*hex-1-enyl acetate, pyrolysis of the latter (Table 2, runs 10—12) yields no evidence

[8] Rodd, "Chemistry of Carbon Compounds," Elsevier, London, 1954, Vol IIa, p. 5; Favorský and Boshowsky, *Annalen*, 1912, **390**, 122; Favorsky, *Bull. Soc. chim. France*, 1936, (v), **3**, 1727.
[9] Hurd and Bennett, *J. Amer. Chem. Soc.*, 1929, **51**, 1197.
[10] See ref. 3, p. 2721.
[11] Chitwood, U.S.P. 2,251,983/1949.
[12] Hurd and Tallyn, *J. Amer. Chem. Soc.*, 1925, **47**, 1779.

for formation of 2-methyl*cyclo*hexanone, which on the above basis should be the ketonic product of a C^1 scission.

C^2 Scission.—The present work adds three examples to the growing list[13] of C^2 scissions, believed until recently to occur only rarely in ester pyrolysis.

Unexplained Products.—The trace of acetone formed from *cyclo*hex-1-enyl acetate, and the larger amount of *cyclo*hexanone from the corresponding benzoate, are presumably due to a complex free-radical mechanism. Since the benzoate was rigorously dried before pyrolysis, a partial hydrolysis by adventitious water cannot be responsible for the concurrent formation of ketone and a trace of benzoic acid. The benzene which is a by-product from the pyrolysis of *cyclo*hex-1-enyl benzoate clearly arises from the aroyl half

TABLE 1. *Pyrolysis of* iso*propenyl acetate* (I; R = R′ = Me) *and acetylacetone* (III; R = R′ = Me).

Pyrolysand	(I; R = R′ = Me)			(III; R = R′ = Me)					
Run No.	1	2	3	4	5	6	7 †	8	9
Temp.	500°	500°	500°	550°	500°	500°	500°	450°	400°
Feed-rate (g./min.)	0·33	0·20	0·19	0·15	0·40	0·20	0·20	0·20	0·14
Contact time (sec.)	14	24	25	30	12	24	24	25	39
Wt. pyrolysed (g.)	60·0	30·0	57·0	50·0	50·0	73·4	50·0	10·0	10·0
(*a*) In cold trap (ml.)	6·0	3·0	6·0	1·5	Nil	Nil	0·5	Nil	Nil
(*b*) In main receiver (g.)	53·6	27·0	53·2	40·0	46·5	62·5	39·1	9·2	9·0
(*c*) Gaseous pyrolysate (l.)	1·8	1·3	2·7	5·3	1·0	4·3	3·8	0·3	0·1
Composition (%) of (*c*) (approx.):									
CO	87	63	80	63	60	59	57	—	—
CO_2	10	20	16	22	20	29	29	—	—
Unsat. hydrocarbons	3	17	4	15	20	12	14	—	—
CH_4	—	—	—	*	—	*	*	—	—
CO : CO_2 (molar ratio)	8·7	3·2	5·0	2·9	3·0	2·0	2·0	—	—

* Traces observed by infrared spectrometry. † Carbonised reaction vessel from Run 6 used.
— Not observed.

TABLE 2. *Pyrolysis of* cyclo*hex-1-enyl acetate* (II; R = Me), cyclo*hex-1-enyl benzoate* (II; R = Ph), 2-*benzoyl*cyclo*hexanone* (IV; R = Ph), *and* cyclo*hexanone; copyrolysis of* cyclo*hexanone and benzoic acid.*

Pyrolysand	(II; R = Me)			(II; R = Ph)			(IV; R = Ph)			*cyclo*Hexanone	
Run No.	10	11	12	13	14	15	16	17	18	Alone 19	With benzoic acid ‡ 20
Temp.	500°	500°	500°	480°	500°	500°	500°	500°	500°	500°	500°
Feed-rate (g./min.)	0·27	0·23	0·51	0·30	0·29	0·22	0·25	0·32	0·25	0·20	0·45
Contact time (sec.)	25	29	13	17	20	44	23	30	38	23	11
Wt. pyrolysed (g.)	30·0	27·0	61·0	40·0	40·0	30·0	14·0	30·0	30·0	32·0	42·6
(*a*) In cold trap (g.)	†	†	†	†	†	2·0	†	Nil	Nil	†	Nil
(*b*) In main receiver (g.)	25·2	24·0	58·0	36·0	39·0	27·0	11·0	21·5	21·4	31·5	41·6
(*c*) Gaseous pyrolysate (l.)	1·7	2·1	2·3	1·5	2·0	4·2	0·5	2·9	4·6	0·25	0·4
Composition (%) of (*c*) (approx.):											
CO	69	63	—	78	85	69	63	71	—	57	60
CO_2	9	9	—	11	9	12	20	16	—	5	9
Unsat. hydrocarbons	22	28	—	11	6	19	17	13	—	38	31
CH_4	—	*	—	—	—	*	—	—	*	—	—
CO : CO_2 (molar ratio)	7·7	7·0	—	7·1	9·4	5·7	3·2	4·4	—	11·4	6·5

* Traces observed by infrared spectrometry. † No cold trap used.
‡ Sat. solution (ketone 25·9 g., acid 16·7 g.). — Not observed.

of the ester molecule, rather than from the *cyclo*alkenyl half by some type of dehydrogenation, since it is not formed from the corresponding acetate, whereas the reverse holds for

[13] For summary, see Mackinnon and Ritchie, *J.*, 1957, 2564.

the formation of *cyclo*hexene. Decarboxylation of benzoic acid formed by the A^2 scission may, of course, contribute to the formation of benzene; but this can be only a minor reaction, since copyrolysis of a mixture of benzoic acid and *cyclo*hexanone, under the same conditions, leads to very little decomposition of either component (Table 2, run 20).

Another product of doubtful origin is ethylene. It has been obtained from vinyl esters [3] and ethers,[14] where free-radical reactions at a vinyl group may be responsible, but in the three present examples it must have some other origin—possibly (for the two acetates) partial breakdown of keten [15] from the major B^1 scission, or (for the two *cyclo*hex-1-enyl esters) breakdown of a labile intermediate such as the postulated *cyclo*hexyne.

Again, though carbon monoxide is produced in quantity by the *cyclo*hex-1-enyl esters, its origin is not immediately clear. Secondary C^1 scission of the primary β-diketones seems to be excluded (see remarks on C^1 scission), but secondary partial breakdown of the observed *cyclo*hexanone may be responsible, since this ketone yields [16] carbon monoxide on pyrolysis (cf. Table 2, run 19). In addition, partial secondary breakdown of keten [15] may contribute to formation of carbon monoxide from the enol acetates. Whatever the source of the carbon monoxide, it is the major component of the gaseous pyrolysate in each case now studied; the $CO : CO_2$ molar ratio always lies within the range *ca.* 2—9 (cf. Tables 1 and 2).

Since several of the observed products might formally originate both from the enol carboxylate and from its isomeric β-diketone, it is difficult to say whether they arise, in practice, from both sides of the equilibrium system or from one only. For example, formation of keten and (enolic) acetone directly from *iso*propenyl acetate (B^1 scission) is strongly favoured by (i) the larger amounts obtained when equilibrium is approached from the ester side, and (ii) the analogous formation of keten from vinyl acetate and *iso*butyrate,[3] whose rearrangement product is here too unstable to be a significant source of the keten. Ambiguity is introduced, however, by the fact (also observed by Hurd and Tallyn [12]) that small amounts of keten and acetone are formed on pyrolysis of pure acetylacetone, which is quite in accordance with the well-known thermal scission of acetone to keten and methane. There is, on the other hand, much less ambiguity if a trace of a substance is detected on pyrolysing (say) the ester but not the corresponding β-diketone, as, for example, in the formation of benzoic acid from *cyclo*hex-1-enyl benzoate, and of ethyl methyl ketone from *iso*propenyl acetate.

Experimental

Apparatus and Procedure.—The system of reaction vessels, traps, and receivers has already been described.[3] Before each run, the flow system was several times evacuated and flushed with nitrogen to avoid combustion effects during pyrolysis; except where otherwise stated, carbonised deposits were removed after each run by heating the vessel to *ca.* 500° in a current of air.

Analytical Methods: Results.—Tables 1 and 2 summarise the general overall conditions and results for 20 runs. Contact times were calculated as previously.[17] The liquid (*a*, *b*) and gaseous (*c*) pyrolysates were analysed by standard chemical methods, supplemented by infrared and ultraviolet spectrometry. In a few cases, where no published infrared spectra could be traced, reference compounds were synthesised and their absorption spectra measured. Keten was characterised as acetanilide (aniline–ether trap), simple aldehydes and ketones as their 2 : 4-dinitrophenylhydrazones (mixed m. p. and/or paper chromatography [18]), acetic acid as acetanilide, and benzene as *m*-dinitrobenzene. Acid anhydrides were detected by the Davidson–Newman colour reaction [19] and by infrared spectrometry. All solids were identified by

[14] Iengar and Ritchie, *J.*, 1956, 3563.
[15] Peytral, *Bull. Soc. chim. France*, 1921, (iv), **31**, 122.
[16] Hurd, "The Pyrolysis of Carbon Compounds," Chemical Catalog Co., New York, 1929, p. 258; Hurd, Greengard, and Roe, *J. Amer. Chem. Soc.*, 1939, **61**, 3359.
[17] Allan, Jones, and Ritchie, *J.*, 1957, 524.
[18] Burton, *Chem. and Ind.*, 1954, 576.
[19] Davidson and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 1515.

mixed m. p. Gases were analysed by the Hempel method: all results are reported on a nitrogen-free basis. In some runs, a trace of methane was detected by infrared spectrometry, though masked by the excess of nitrogen during Hempel analysis.

Preparation of Pyrolysands.—iso*Propenyl acetate*. Pure ester (L. Light & Co. Ltd.) was redistilled: the fraction used had b. p. 92—94°, n_D^{20} 1·406.

Acetylacetone. Pure diketone (L. Light & Co. Ltd.) was redistilled: the fraction used had b. p. 134—139°, n_D^{18} 1·452.

cyclo*Hex*-1-*enyl acetate*. The ester, prepared as described by Bedoukian,[20] had b. p. 180—182°, 92°/34 mm., and n_D^{20} 1·464 (lit.,[20] b. p. 74—76°/17 mm., n_D^{25} 1·4585) (Found: C, 68·6; H, 8·8. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·6%). The ester showed major infrared absorption bands at *ca.* 2941s, 2857m, 1767s, 1695m, 1449m, 1443m, 1366s, 1217s, 1121s, 1073m, 1043m, 1010m, and 905m cm.$^{-1}$.

cyclo*Hex*-1-*enyl benzoate*. Attempts to prepare this compound by ester-interchange between *cyclo*hex-1-enyl acetate and benzoic acid, or by direct Schotten–Baumann benzoylation of (enolic) *cyclo*hexanone, were unsuccessful. Ultimately, it was prepared as described by Nesmeyanov, Lutsenko, and Tumanova.[21] *cyclo*Hex-1-enyl acetate was converted into 2-chloromercuri*cyclo*hexanone (m. p. 134—135°) which was dried and treated with freshly distilled benzoyl chloride in sodium-dried xylene (50°; 12 hr.; rapid stirring). The product was fractionated, washed free from mercuric chloride (dilute ammonia), and refractionated, yielding pure (II; R = Ph), b. p. 138—142°/2 mm., 144—145°/7 mm., n_D^{20} 1·547 (lit.,[21] b. p. 146—147°/6 mm., n_D^{20} 1·5386) (Found: C, 77·1; H, 7·2. Calc. for $C_{13}H_{14}O_2$: C, 77·2; H, 6·9%). It appears that the use of rigorously dry xylene is important; this precaution led to yields of *ca.* 40% (Nesmeyanov *et al.*[21] claim 63%), whereas various preparations in which ordinary technical xylene was used gave yields of only *ca.* 5—10%. The ester showed major infrared absorption bands at *ca.* 1730s, 1595m, 1308(shoulder), 1250s, 1215(shoulder), 1120s, 1068m, 1029m, and 710m cm.$^{-1}$.

2-*Benzoyl*cyclo*hexanone*. This was prepared as described by Hauser, Ringler, Swarmer, and Thomson,[22] who claim a yield of 69%. Preliminary work gave very low yields, but the use of 3 instead of 2 equiv. of fresh sodamide, with heating for 12 hr. (water-bath), gave a yield of 22%. The diketone had m. p. 88—89° (needles from ethanol or light petroleum: lit.,[22] m. p. 88—89°) and b. p. 160—166°/1 mm. (Found: C, 77·2; H, 7·3. Calc. for $C_{13}H_{14}O_2$: C, 77·2; H, 6·9%). It showed major infrared absorption bands at *ca.* 1709s, 1672s, 1600 m, 1580m, 1361s, 1316m, 1282s, 1250s, 1236s, 1183s, 1129s, 1104m, 1072m, 958m, 913m, 787m, 744s, 693m, and 684s cm.$^{-1}$.

Preparation of Reference Compounds for Infrared Spectrometry.—1-*Methyl*cyclo*hexene*. The olefin, prepared as described by Sabatier and Mailhe,[23] had b. p. 110—112°, n_D^{18} 1·458 (lit.,[23] b. p. 110·5—111°, n_D^{12} 1·458) and showed major infrared absorption bands at *ca.* 1442s, 1370m, 1305m, 1260m, 1135s, 1089s, 1050s, 1014s, 960m, 910s, 890s, 855m, 820s, 790s, and 750s cm.$^{-1}$, in good agreement with published figures.[24]

1-*Phenyl*cyclo*hexene*. Prepared as described by Sabatier and Mailhe,[23] it had b. p. 126—128°/18 mm., n_D^{14} 1·569 (lit.,[23] b. p. 129—130°/20 mm., n_D^{14} 1·5676) (Found: C, 91·2; H, 9·2. Calc. for $C_{12}H_{14}$: C, 91·1; H, 8·9%) and showed major infrared absorption bands at *ca.* 1600m, 1494s, 1445s, 754s, 734s, and 685m, cm.$^{-1}$.

Pyrolysis of iso*Propenyl Acetate.*—*Runs* 1—3. The analytical results of these runs were similar; those for Run 1 are given as typical. Liquid (*a*) contained acetone. Liquid (*b*), distilled, yielded eight fractions, (i) 6·2 g., b. p. 60—86°, (ii) 7·1 g., b. p. 86—100°, (iii) 13·3 g., b. p. 100—126°, (iv) 20·3 g., b. p. 126—148°, (v) 1 g., b. p. 148—164°, (vi) *ca.* 1 g., b. p. 48—60°/1·3 mm., (vii) *ca.* 0·5 g., b. p. 60—84°/1·3 mm., and (viii) *ca.* 0·2 g., b. p. 84—96°/1·3 mm. There was a small tarry residue. Fractions (i), (ii), and (iii) contained acetone, ethyl methyl ketone, and acetic acid respectively. Fraction (iv) contained acetylacetone (semicarbazone) and an acid anhydride (colour reaction [19]); fraction (v) was similar. Fractions (vi) and (vii) appeared to be mainly acetylacetone contaminated with a little tar. The exit gases (*c*) contained keten (aniline–ether trap), together with methylacetylene, ethylene, and a

[20] Bedoukian, *J. Amer. Chem. Soc.*, 1945, **67**, 1430.
[21] Nesmeyanov, Lutsenko, and Tumanova, *Izvest. Akad. Nauk, S.S.S.R., Otdel. khim. Nauk*, 1949, 601.
[22] Hauser, Ringler, Swarmer, and Thomson, *J. Amer. Chem. Soc.*, 1947, **69**, 2649.
[23] Sabatier and Mailhe, *Compt. rend.*, 1904, **138**, 1321.
[24] Amer, Petroleum Inst., Research Project 44, Nat. Bur. Stand., Washington, Serial No. 897, 1949.

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trace of methane (infrared). There was no evidence for allene, and *iso*butene could not be detected with certainty. However, the authors are indebted to Dr. R. G. A. New for additional results observed in the Blackley Laboratories of Imperial Chemical Industries Limited, where it was found that liquid (*a*) from the cold trap (several runs, bulked), on fractionation in a Podbielniak column, yielded allene (b. p. −32°), methylacetylene (b. p. −23°), and *iso*butene (b. p. −6°). These fractions were separately brominated, and the bromo-derivatives identified; in addition, the silver salt of methylacetylene was prepared from the second fraction. (Dr. New's results confirm the present work in all other details.)

Pyrolysis of Acetylacetone.—Runs 4—6. The analytical results for Run 4 are given as typical. Liquid (*a*) was mainly acetone. Liquid (*b*), distilled, yielded five fractions, (i) 13·1 g., b. p. 54—72°, (ii) 0·7 g., b. p. 82—100°, (iii) 2·2 g., b. p. 110—130°, (iv) 20·1 g., b. p. 130—150°, and (v) 1·0 g., b. p. 150—160°. There was a small tarry residue. Fraction (i) was mainly acetone; there was no evidence for ethyl methyl ketone in fraction (ii), and evidence for *iso*propenyl acetate (infrared, ultraviolet) was inconclusive (see, however, Run 7); fraction (iii) contained acetic acid; fractions (iv) and (v) were mainly unchanged acetylacetone, containing a little acetic anhydride (colour reaction [19]). The exit gases (*c*) contained keten.

Run 7. Liquid (*a*) contained acetone; the exit gases (*c*) contained keten. Liquid (*b*), dissolved in ether, was washed free from acid with aqueous sodium hydrogen carbonate; the ether layer, dried and freed from ether, yielded four fractions on distillation: (i) *ca.* 0·5 g., b. p. 54—86°, (ii) *ca.* 0·7 g., b. p. 86—100°, (iii) *ca.* 0·8 g., b. p. 100—110°, and (iv) *ca.* 1 g., b. p. 110—112°. There was a small tarry residue. Fractions (i)—(iii) contained unchanged acetylacetone (ultraviolet absorption band, $\lambda_{max.}$ 273), together with *iso*propenyl acetate (ultraviolet absorption band, $\lambda_{max.}$ 206, and infrared bands at *ca.* 1745 and 1200 cm.$^{-1}$). Control experiments showed that these bands characteristic of *iso*propenyl acetate persisted strongly when a sample of pure ester was progressively diluted, down to a concentration of 8%, by addition of acetylacetone. Also, a control sample of pure acetylacetone, treated as above with ether and aqueous sodium hydrogen carbonate, showed none of the absorption bands of the ester, showing that the observed enol carboxylate was not produced by an alkali-catalysed rearrangement of the diketone. The exit gases (*c*), passed through ammoniacal cuprous chloride, gave a red precipitate; the presence of methylacetylene was confirmed by observation of infrared absorption bands at *ca.* 2155m, 1462m, 1452m, 1269w, and 920w cm.$^{-1}$ (lit.,[25] 2160, 1459, 1448, 1264, and 921 cm.$^{-1}$). Ethylene and a trace of methane were also present.

Runs 8 *and* 9. Below 500° pyrolysis was very slight; there was almost no carbonisation in the reaction vessel, and no trace of *iso*propenyl acetate in the pyrolysate (*b*).

Pyrolysis of cyclo*Hex*-1-*enyl Acetate.—Run* 10. The exit gases contained keten, acetone vapour (2 : 4-dinitrophenylhydrazine trap), and ethylene and methane (infrared). Liquid (*b*), distilled, yielded six fractions: (i) 1·0 g., b. p. 74—90°, (ii) 0·8 g., b. p. 90—130°, (iii) 2·0 g., b. p. 130—150°, (iv) 6·5 g., b. p. 150—160°, (v) 8·5 g., b. p. 86—100°/28 mm., and (vi) 6·0 g., b. p. 110—114°/28 mm. There was a small tarry residue (*ca.* 0·5 g.). Fraction (i) contained acetone; there was also evidence for an olefin (ultraviolet). Fraction (ii) contained acetic acid and anhydride (infrared); fraction (iii) contained acetic anhydride (infrared; colour reaction [19]) and *cyclo*hexanone; fraction (iv) contained acetic anhydride (trace), *cyclo*hexanone, and unchanged pyrolysand (infrared). (Separate tests showed that although the *pure* pyrolysand yields *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, owing to its partial hydrolysis by the test reagent even in the cold, this source of possible error is eliminated if the ketone is first separated from the rest of the fraction by aqueous sodium hydrogen sulphite, hydrolysis of the ester under these conditions being negligible.) Fraction (v) was unchanged pyrolysand, and fraction (vi) 2-acetyl*cyclo*hexanone. On treatment with semicarbazide hydrochloride, fraction (vi) yielded a crystalline derivative, m. p. 156—157° [Found: C, 60·1; H, 7·0; O (direct), 8·7; *M* (cryoscopic in benzene), 203, 182]; an authentic sample of 2-acetyl*cyclo*hexanone, prepared as described by Levine *et al.*[26] (b. p. 110°/19 mm., n_D^{20} 1·510; lit.,[27] b. p. 111—112°/18 mm., n_D^{20} 1·5138), yielded the same derivative, m. p. and mixed m. p. 157—159°. Leser [27] has described a so-called semicarbazone of (IV; R = Me), m. p. 159°; in a later paper [28] he gives m. p. 162—163°, but in neither case is an analysis reported. It is now clear that the derivative is

[25] Amer. Petroleum Inst., Research Project 44, Nat. Bur. Stand., Washington, Serial No. 45, 1943.
[26] Levine, Conroy, Adams, and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1510.
[27] Leser, *Compt. rend.*, 1905, **141**, 1032.
[28] *Idem, Ann. Chim.* (*France*), 1912, **26**, 233.

not, in fact, the expected semicarbazone, but a dehydration product thereof (Calc. for $C_9H_{13}ON_3$: C, 60·3; H, 7·3; O, 8·9; N, 23·5%; *M*, 179. Calc. for $C_9H_{15}O_2N_3$: C, 54·8; H, 7·7; O, 16·2; N, 21·3%; *M*, 197). The compound loses its nitrogen, on analysis, with some difficulty, and reliable figures could not be obtained (Found: N, *ca.* 20% by micro-Dumas, *ca.* 10% by micro-Kjeldahl). There are several formal possibilities for cyclodehydration of the semicarbazone; it is hoped to publish a note on this compound.

Run 11. This gave similar results; in addition, the first fraction (1·5 g., b. p. 40—72°) obtained by distillation of liquid (*b*) contained 1-methyl*cyclo*hexene (its infrared spectrum showed all the 15 absorption bands listed above for the pure olefin) and *cyclo*hexene (infrared).

Run 12. Liquid (*b*), distilled, yielded seven fractions, (i) 0·5 g., b. p. 56°, (ii) 2·0 g., b. p. 78°, (iii) 0·8 g., b. p. 78—130°, (iv) 2·0 g., b. p. 130—150°, (v) 3·8 g., b. p. 150—160°, (vi) 40·2 g., b. p. 62—88°/24 mm., and (vii) 5·7 g., b. p. 106—110°/24 mm. There was a small tarry residue (*ca.* 1·0 g.). Fraction (i) contained acetone. Fraction (ii), treated with tetranitromethane,[29] gave a yellow colour (*cyclo*hexene gives a yellow and *cyclo*hexa-1 : 3-diene a red colour); redistilled, fraction (ii) had b. p. 78—81°, n_D^{20} 1·440, and yielded adipic acid on oxidation (alkaline permanganate), confirming the presence of *cyclo*hexene. Fraction (ii) also contained a trace of acetone and *cyclo*hexanone. Fractions (iii)—(vii) confirmed the results from Run 10.

In Runs 10—12, 2-methyl*cyclo*hexanone was carefully sought by paper chromatography [18] of the mixed 2 : 4-dinitrophenylhydrazones of the overall ketonic products, the 2 : 4-dinitrophenylhydrazone of this ketone being used as control; no evidence for its presence could be obtained.

Pyrolysis of cyclo*Hex*-1-*enyl Benzoate.—Runs* 13 *and* 14. These two exploratory runs gave similar results; those of Run 13 are given here. Liquid (*b*) slowly deposited a few long needles of 2-benzoyl*cyclo*hexanone, m. p. 89—91° (Found: C, 77·4; H, 7·1. Calc. for $C_{13}H_{14}O_2$: C, 77·3; H, 6·9%). Distillation of the filtrate gave three fractions, (i) 5 g., b. p. 42—140°/1 mm., (ii) 18 g., b. p. 140—160°/1 mm., (iii) 5 g., b. p. 160—166°/1 mm., and 4 g. of tar. Fraction (i) contained *cyclo*hexanone; fraction (ii) was mainly unchanged pyrolysand; fraction (iii) was 2-benzoyl*cyclo*hexanone, which solidified on standing, and yielded the pure diketone on recrystallisation, m. p. 89—91° (Found: C, 77·4; H, 7·1%).

Run 15. Liquid (*a*) was mainly benzene, though surprisingly a little *cyclo*hexanone was also found in the cold trap. Liquid (*b*), distilled, yielded seven fractions, (i) 6·2 g., b. p. 78—84°, (ii) 1·7 g., b. p. 84—144°, (iii) 1·4 g., b. p. 144—148°, (iv) 0·9 g., b. p. 20—90°/3 mm., (v) 1·5 g., b. p. 90—120°/3 mm., (vi) 8·7 g., b. p. 120—140°/3 mm., and (vii) 4·0 g., b. p. 140—164°/3 mm. There was *ca.* 1·5 g. of tarry residue. Fraction (i) was mainly benzene, with a little *cyclo*hexanone; fractions (ii) and (iii) were mainly *cyclo*hexanone. Fraction (iv) contained 1-phenyl*cyclo*hexene; its infrared spectrum showed all the 6 absorption bands listed above for the pure olefin. Fraction (v) was mainly unchanged pyrolysand (infrared), from which a trace of benzoic acid separated during the distillation; fractions (vi) and (vii) consisted of a mixture of unchanged pyrolysand (*ca.* 4·5 g.; infrared) and 2-benzoyl*cyclo*hexanone (*ca.* 8·2 g.), the latter separating out on standing.

Pyrolysis of 2-*Benzoyl*cyclo*hexanone.—Runs* 16—18. These three runs gave similar analytical results; those of Run 16 are given as typical. Liquid (*b*) was filtered free from suspended unchanged pyrolysand; the filtrate, distilled, yielded five fractions, (i) 2·3 g., b. p. 78—84°, (ii) 2·5 g., b. p. 84—168°, (iii) 1·6 g., b. p. 76—130°/2 mm., (iv) 4·4 g., b. p. 130—150°/2 mm., and (v) 1·1 g., b. p. 150—162°/2 mm. There was a small tarry residue (*ca.* 2 g.). Fraction (i) was mainly benzene (characterised as *m*-dinitrobenzene), containing no *cyclo*hexa-1 : 3-diene (infrared; no adduct with maleic anhydride); fraction (ii) was mainly *cyclo*hexanone. Fraction (iii) contained *cyclo*hex-1-enyl benzoate (infrared spectrum showed all 10 absorption bands listed above for the pure ester), 1-phenyl*cyclo*hexene (infrared spectrum showed all 6 absorption bands listed above for the pure olefin), but no benzoic acid. Fractions (iv) and (v) solidified on standing, and consisted of unchanged pyrolysand. The exit gases (*c*) contained ethylene (infrared).

Pyrolysis of cyclo*Hexanone.—Run* 19. Liquid (*b*) was substantially unchanged pyrolysand; a little water was observed, probably due to self-condensation of the ketone to *cyclo*hexylidene-*cyclo*hexanones.[16] The CO : CO_2 ratio in (*c*) was very high.

Copyrolysis of cyclo*Hexanone and Benzoic Acid.—Run* 20. Liquid (*b*) (which became red

[29] Werner, *Ber.*, 1909, **42**, 4325; Kaufmann, King, and Huang, *Ber.*, 1942, **75**, 1201.

on standing overnight) was substantially unchanged pyrolysand; a little water was observed (cf. Run 19). The colour test [19] for acid anhydride gave a negative reaction.

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950. α-1 : 4-*Glucosans. Part VIII.* Multiple-branching in Glycogen and Amylopectin.*

By A. MARGARET LIDDLE and D. J. MANNERS.

The degree of multiple-branching in a glycogen or amylopectin can be evaluated from the chain lengths of the corresponding muscle-phosphorylase and β-amylase limit dextrins.

Fifteen samples of glycogen, from various biological sources, show small but significant differences in degree of multiple-branching. Amylopectins show a similar range of values. Accordingly, the marked physicochemical differences between glycogen and amylopectin cannot be related to differences in degree of multiple-branching.

A RECENT development in the chemistry of glycogen and amylopectin has been the recognition that multiple-branching is a characteristic structural feature. Multiple-branching was first postulated by Meyer,[1] and has been confirmed experimentally by Peat [2] and Cori [3] and their respective co-workers. We now describe a method for the quantitative estimation of the degree of multiple-branching in a branched α-1 : 4-glucosan. A preliminary account of part of this work has been published.[4]

The degree of multiple-branching may be conveniently expressed as the ratio ($\overline{A/B}$) of A-chains to B-chains. An A-chain (side-chain) is linked to the molecule only by the reducing group, whilst B-chains (main-chains) which are similarly linked, also have other chains attached to them.[2] In a glycogen-type molecule containing x chains, $\overline{A/B} = 1 : (x - 1)$ for a singly-branched " laminated " structure of the type originally suggested by Haworth, Hirst, and Isherwood,[5] whereas a multiply-branched " tree " structure as postulated by Meyer [1] contains approximately equal numbers of A- and B-chains.

For the proposed method of estimation of $\overline{A/B}$, a knowledge of the average chain length ($\overline{CL}$), muscle-phosphorolysis limit and β-amylolysis limit is required. From these, the difference (Δ) in $\overline{CL}$ values of the phosphorylase limit dextrin (ϕ-dextrin) and the β-amylase limit dextrin (β-dextrin) can be calculated. Normally, muscle phosphorylase removes 30—40% of glycogen as α-D-glucosyl phosphate, and β-amylase 40—50% as maltose, this degradation being limited to the exterior chains of the polysaccharide. The observed value Δ can be related to $\overline{A/B}$ as follows: in a β-dextrin, A-chain " stubs " contain 2 or 3 glucose residues,[2] whilst B-chain " stubs," which are probably of a similar

* Part VII, *J.*, 1957, 4430.

[1] Meyer and Bernfeld, *Helv. Chim. Acta*, 1940, **23**, 875; Meyer and Fuld, *ibid.*, 1941, **24**, 375.
[2] Peat, Whelan, and Thomas, *J.*, 1952, 4546; *J.*, 1956, 3025.
[3] Larner, Illingworth, G. T. Cori, and C. F. Cori, *J. Biol. Chem.*, 1952, **199**, 641.
[4] Liddle and Manners, *Biochem. J.*, 1955, **61**, xii.
[5] Haworth, Hirst, and Isherwood, *J.*, 1937, 577.

length, are considered to contain n glucose residues. In a ϕ-dextrin, the A-chain " stubs " contain a single glucose residue, whereas the B-chain " stubs " contain 4 glucose residues more than those of the corresponding β-dextrin, *i.e.* $(4 + n)$.[6] In a branched α-1 : 4-glucosan with $\overline{A/B} = 1 : 1$, the average length of the exterior chains in the ϕ-dextrin is $[1 + (4 + n)]/2$, and in the β-dextrin is $(n + 2{\cdot}5)/2$, *i.e.* $\Delta = 1{\cdot}25$ glucose residues. [It will be noted that this calculation is independent of the length of the B-chain " stub " of a β-dextrin.] Similarly, when $\overline{A/B} = 1 : 2$, the exterior chain lengths of the ϕ- and β-dextrins are $[1 + 2(4 + n)]/3$ and $(2{\cdot}5 + 2n)/3$ so that $\Delta = 2{\cdot}17$. The values of Δ in the range $\overline{A/B} = 2 : 1 \longrightarrow 1 : 8$ have been calculated, and a graph of Δ against $\overline{A/B}$ prepared. The degree of multiple-branching can therefore be evaluated from experimental determinations of Δ.

In the present study, 15 samples of glycogen and 2 of amylopectin have been examined. Values of $\overline{CL}$ were determined by oxidation with potassium periodate,[7] and the β-amylolysis experiments are described in Part VI of this Series.[8] The polysaccharides were then incubated with rabbit-muscle phosphorylase [9] in presence of 0·1M-phosphate (pH 6·8) and 0·001M-adenylic acid (activator), and the percentage conversion into α-D-glucosyl phosphate determined. Control experiments showed that the enzyme was free from α-amylase and amylo-1 : 6-glucosidase (the " debranching " enzyme of rabbit muscle [6]), so that enzyme action must be confined to the outer chains of the polysaccharide. Although phosphorolysis was continued for 24 hr., enzyme action, with 90 ± 15 units * of phosphorylase per mg. of substrate, was complete within 1·5 hr.; moreover, the phosphorolysis limits were not altered by a four-fold increase in initial enzyme concentration, or by the addition of fresh enzyme after 4 hr. Since the enzyme was dissolved in a 0·03M-cysteine–1% glycerophosphate buffer, the amount of cysteine (traces of which are required for maximum solubilisation and activity of the enzyme [9]) could not be a limiting factor. Under these conditions, 14—36% of various glycogens and 40—41% of the amylopectin samples were converted into α-D-glucosyl phosphate. It will be noted that *Helix pomatia* II glycogen and rabbit liver I glycogen, both of which have low β-amylolysis limits,[8] have phosphorolysis limits of only 22 and 14%, respectively.

Comparable calculations based on phosphorolysis and β-amylolysis results published by G. T. Cori and her co-workers [3] show that rabbit liver glycogen, wheat amylopectin, and corn amylopectin have Δ values of 1·8, 2·6, and 2·7, respectively, equivalent to $\overline{A/B} = 1 : 1{\cdot}5$, $1 : 2{\cdot}9$, and $1 : 3{\cdot}2$.

It is concluded that different glycogens show small but significant differences in multiple-branching. The variation in $\overline{A/B}$ values is greater than that caused by a small experimental error in the analytical procedures. For example, if the phosphorolysis and β-amylolysis limits of rabbit liver I glycogen were 15 and 24%, respectively, then Δ would be 1·1, equivalent to $\overline{A/B} = 1 : 0{\cdot}9$; alternatively, if the limits were 13 and 26%, respectively, then the calculated $\overline{A/B}$ value is $1 : 1{\cdot}4$. Both of these $\overline{A/B}$ values are significantly different from those of the other rabbit liver glycogens.

Our previous studies [7,8] have already shown that glycogens differ in degree and position of branching, and it now seems clear that variations in degree of multiple-branching also exist. These properties do not appear to be related to the biological source of the glycogen. Furthermore, amylopectins show small variations in $\overline{A/B}$, over a similar range of values.

The above results are in agreement with other studies on multiple-branching. Calculations based on the yield of (*a*) maltose and maltotriose liberated by the action of

* For definition, see ref. 9.

[6] Cori and Larner, *J. Biol. Chem.*, 1951, **188**, 17.
[7] Bell and Manners, *J.*, 1952, **3641**; Manners and Archibald, *J.*, 1957, 2205.
[8] Liddle and Manners, *J.*, 1957 3432.
[9] Green and G. T. Cori *J. Biol. Chem.*, 1943, **151**, 21; Illingworth and G. T. Cori, *Biochem. Preparations*, 1953, **3**, 1.

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R-enzyme on amylopectin β-dextrin [2] and (*b*) glucose liberated from a glycogen or amylopectin ϕ-dextrin by amylo-1 : 6-glucosidase [10] indicate that all these polysaccharides contain a high proportion of A-chains, $\overline{A/B}$ ranging from *ca.* 1 : 1 to 1 : 3. The marked physicochemical differences [10] between glycogen and amylopectin (*e.g.* molecular shape,

Multiple-branching in glycogen and amylopectin.

Polysaccharide	$\overline{CL}$	ϕ-limit (%)	$\overline{CL}$ of ϕ-dextrin	β-limit (%)	$\overline{CL}$ of β-dextrin	Δ	$\overline{A/B}$
Glycogens							
Rabbit liver I	13	14	11·2	25	9·8	1·4	1 : 1·1
,, III	13	31	9·0	51	6·4	2·6	1 : 2·9
,, V	14	32	9·5	51	6·9	2·6	1 : 2·9
,, XIII	15	30	10·5	46	8·1	2·4	1 : 2·4
Cat liver IV	13	36	8·3	53	6·1	2·2	1 : 2·0
,, VI	12	34	7·9	52	5·8	2·1	1 : 1·9
Fœtal sheep liver	13	29	9·2	49	6·6	2·6	1 : 2·9
Rabbit muscle I	13	25	9·8	45	7·2	2·6	1 : 2·9
Human muscle II	11	22	8·6	40	6·6	2·0	1 : 1·8
Mytilus edulis V	9	21	7·1	40	5·4	1·7	1 : 1·4
,, VI	13	28	9·4	46	7·0	2·4	1 : 2·4
Ascaris lumbricoides	12	31	8·3	49	6·1	2·2	1 : 2·0
Helix pomatia II	7	22	5·5	37	4·4	1·1	1 : 0·9
Tetrahymena pyriformis I	13	31	9·0	44	7·3	1·7	1 : 1·4
Brewer's yeast	13	30	9·1	44	7·3	1·8	1 : 1·5
Amylopectins							
Waxy maize starch	20	41	11·8	50	10·0	1·8	1 : 1·6
Waxy sorghum starch	22	40	13·2	52	10·6	2·6	1 : 2·9

interaction with iodine and with concanavalin-A) are therefore not directly due to different degrees of multiple-branching, but arise from different conformations of A- and B-chains. This latter probably reflect differences in the site and mode of biosynthesis of the polysaccharides. In the animal cell, glycogen synthesis appears to be a three-dimensional polymerisation, whilst that of amylopectin must be sterically limited during the formation of mixed layers of amylose and amylopectin in the starch granule.

Experimental

Analytical Methods.—Inorganic phosphate was estimated by Allen's colorimetric method,[11] except that a 10% solution of ammonium molybdate was used.

For the estimation of α-D-glucosyl phosphate in presence of 0·1M-inorganic phosphate a modification of Hanes's method [12] has been used. Aliquot parts of the enzyme digests (2 ml.) were diluted with distilled water (2 ml.), and magnesia solution [0·86% (w/v) magnesium chloride hexahydrate, 1·35% (w/v) ammonium chloride, 3·5% (v/v) aqueous ammonia; 10 ml.] was added, the mixture being warmed to *ca.* 50°. After about 45 min., the mixture was diluted to 25 ml. and the magnesium ammonium phosphate precipitate removed. An aliquot part of the filtrate (5 ml.) was hydrolysed with 11N-hydrochloric acid (0·65 ml.) for 7 min. at 98°, the solution cooled and diluted to 25 ml., and the inorganic phosphate content measured. A portion of the original filtrate, without acid hydrolysis, was also examined. Control experiments showed that glucose 6-phosphate was not hydrolysed under these conditions, and that adsorption of α-D-glucosyl phosphate on the magnesium ammonium phosphate precipitate did not occur. By contrast, if the inorganic phosphate is precipitated without dilution at room temperature, coprecipitation of the α-D-glucosyl phosphate occurs.

Phosphorylase.—Rabbit muscle phosphorylase was prepared by methods similar to those of Green and Cori, and Illingworth and Cori.[9] Several preparations were made; they varied in degree of crystallinity, and in the relative proportion of *a* and *b* forms. The phosphorylase was stored at 0° in 0·03M-cysteine hydrochloride–1% sodium β-glycerophosphate buffer.

We are indebted to Professor C. H. Waddington, F.R.S., and Dr. R. A. Beatty for the

[10] Manners, *Adv. Carbohydrate Chem.*, 1957, **12**, 261.
[11] Allen, *Biochem. J.*, 1940, **34**, 858.
[12] Hanes, *Proc. Roy. Soc.*, 1940, *B*, **128**, 426.

supply of rabbits, and to Mrs. R. M. Clayton who anæsthetised the rabbits; in some preparations, magnesium sulphate [13] was used in place of Nembutal.

Phosphorolysis of Polysaccharides.—Digests were prepared containing brewer's yeast glycogen [11] (40—50 mg.), 0·5M-phosphate buffer (pH 6·8; 4 ml.), 0·01M-adenylic acid (2 ml.), and phosphorylase solution (7500 units/ml.; 0·5 or 2·0 ml.) in a total volume of 20 ml. After incubation at 35°, portions (2 ml.) were removed for determination of α-D-glucosyl phosphate.

Time of incubation (hr.)	0·02	1·0	5·0	24·0
Phosphorolysis (%)				
(*a*) 80 units/mg. of glycogen	5	30	30	30
(*b*) 320 units/mg. of glycogen	19	31	31	29

In a subsequent experiment, glycogen (from *Helix pomatia*) on incubation with 110 units of phosphorylase/mg. gave 20% conversion into α-D-glucosyl phosphate within 1 hr. After 4 hr. the enzyme concentration was increased to 250 units/mg.; no further degradation occurred in the following 20 hr.

The phosphorolysis limits of the polysaccharides were determined, in duplicate, 75—105 units of phosphorylase/mg. of substrate being used. The α-D-glucosyl phosphate contents of samples of the digests examined after incubation for 1·5, 3, and 24 hr. were identical, or differed by only 1%.

Under the above conditions, normal mammalian glycogens had phosphorolysis limits of 29—36% and isolated ϕ-dextrins were resistant to further enzyme action. With less active enzyme preparations, the percentage conversions into α-D-glucosyl phosphate were 20—25%.[14]

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DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, July 5th,* 1957.]

[13] Campbell, *Biochem. J.*, 1952, **52**, 444.
[14] Cf. Manners and Khin Maung, *J.*, 1955, 867.

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951. *Alkenylation with Lithium Alkenyls. Part XIV.* Syntheses in the* cyclo*Octene Series.*

By (the late) E. A. BRAUDE, W. F. FORBES, B. F. GOFTON, R. P. HOUGHTON, and E. S. WAIGHT.

The direct metallation of 1-chloro- and 1-bromo-*cyclo*octene by lithium, the reactions of the lithium alkenyl with aldehydes and ketones, and various reactions of the resulting alcohols are described. The results are generally similar to those observed with the smaller ring systems, except that the double bond shows a greater degree of stability in the endocyclic position.

IN earlier papers, a variety of syntheses based on lithium alkenyls of the five-, six-, and seven-membered *cyclo*alkene series have been described.[1-4] This and the following paper deal with derivatives of the " medium-sized " *cyclo*octene and *cyclo*decene ring systems.

The preparation of 1-chloro- and 1-bromo-*cyclo*octene from the 1 : 2-dihalogeno*cyclo*octanes has been described by Kohler *et al.*[5] The action of chlorine on *cis-cyclo*octene in chloroform without special precautions gives a mixture of di- and tri-chloro*cyclo*octanes

* Part XIII, *J.*, 1956, 3333.

[1] Braude and Forbes, *J.*, 1951, 1755.
[2] Braude and Coles, *J.*, 1950, 2014.
[3] Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1414, 1419; Ginsburg, *J.*, 1954, 2361; Braude and Evans, *J.*, 1955, 3334.
[4] Braude, Forbes, and Evans, *J.*, 1953, 2202.
[5] Kohler, Tishler, Potter, and Thompson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.

(presumably by allylic substitution before addition, as has also been observed with *cyclo*hexene [6]) but, on exclusion of oxygen, 1 : 2-dichloro*cyclo*octane is the principal product; the reaction with bromine appears much less susceptible to catalytic influences, probably because addition is more rapid. The Hofmann elimination reaction of the 1 : 2-halogeno-*cyclo*octanes by Kohler's method [5] afforded good yields of the 1-halogeno*cyclo*octenes. Although this method of synthesis could lead to the *trans-cyclo*octene derivatives (*trans*-addition to the *cis*-ring, followed by *trans*-elimination of hydrogen halide), the properties of these 1-halogeno*cyclo*octenes leave no doubt that they are the *cis*-ring isomers; in the eight-membered series, only the parent hydrocarbon has as yet been obtained [7] in the *trans*-configuration.

An alternative preparation of 1-chloro*cyclo*octene, by the action of phosphorus pentachloride on *cyclo*octanone, has been reported by Domnin.[8] This is the method preferred for the lower homologues and it has been suggested [1] that it involves elimination of $HO{\cdot}PCl_4$ from an intermediate of the type $>CCl{\cdot}O{\cdot}PCl_4$, which can readily undergo *trans*-1 : 2-elimination leading to the *cis*-1-chloro*cyclo*alkene. We have confirmed that the products obtained by Kohler's and Domnin's procedures are identical, though the success of the latter method is very dependent on the purity of the *cyclo*octanone; low-melting ketone, of about 80% purity (based on gas–liquid chromatographic analysis), gives a product from which no pure 1-chloro*cyclo*octene can be isolated, and which cannot be successfully used for reactions involving conversion into *cyclo*octenyl-lithium.

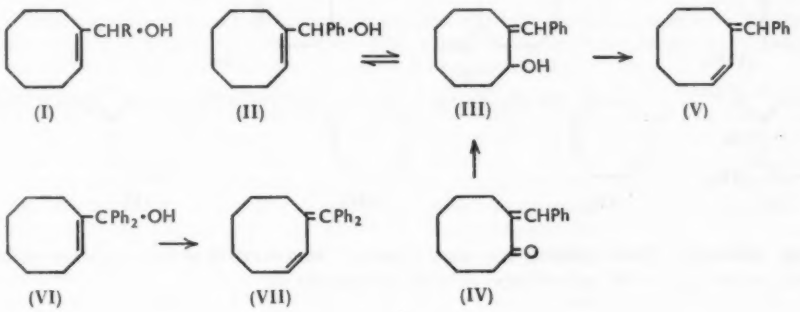
The metallation of 1-bromo*cyclo*octene by lithium and the carboxylation of the resulting lithium alkenyl has already been effected by Cope, Burg, and Fenton.[9] *cyclo*Oct-1-enyl lithium from 1-chloro*cyclo*octene is formed less readily, but with an ease comparable to that of the lower homologues, and the same *cyclo*oct-1-enecarboxylic acid is obtained in each case and in nearly identical yield.

The lithium alkenyl prepared from 1-chloro- or 1-bromo-*cyclo*octene also reacts in the normal manner with aldehydes and ketones, to give alcohols in 25—65% yields. 1-Hydroxymethyl*cyclo*octene (I; R = H) (from formaldehyde) and 1-1′-hydroxyethyl*cyclo*octene (I; R = Me) (from acetaldehyde) were characterised as 3 : 5-dinitrobenzoates, and the hydroxyethyl compound was oxidised by chromic oxide in pyridine to 1-acetyl*cyclo*octene. The latter showed normal ultraviolet light absorption ($\lambda_{max.}$ 2360 Å, ε 11,500; cf. 1-acetyl*cyclo*hexene [10]) and on catalytic hydrogenation furnished acetyl*cyclo*octane.

With benzaldehyde the lithium alkenyl gave α-(*cyclo*oct-1-enyl)benzyl alcohol (II), the structure of which was confirmed by oxidation to the known [11] *cyclo*oct-1-enyl phenyl ketone. On treatment with dilute acid, the alcohol (II) underwent oxotropic rearrangement to 2-benzylidene*cyclo*octanol (III), but the intensity of light absorption at 2500 Å, which rose to a constant value (ε 8000), was lower than that expected for complete conversion; further, the material obtained on oxidation of this product showed maxima (at 2500 and 2830 Å) which suggested the presence of the two ketones derived from (II) and (III). Pure 2-benzylidene*cyclo*octanone (IV), showing the expected high-intensity absorption maxima, was prepared by condensation of benzaldehyde with *cyclo*octanone in the presence of boiling aqueous potassium hydroxide; under milder conditions the intermediate aldol could be isolated, and was readily converted into the unsaturated ketone by treatment with naphthalenesulphonic acid. Reduction of this ketone with lithium aluminium hydride gave pure 2-benzylidene*cyclo*octanol (III), and when this was treated with dilute acid it gave the same equilibrium mixture as that obtained from the isomer (II). Dehydration of 2-benzylidene*cyclo*octanol with naphthalenesulphonic acid

[6] Bloomfield, *J.*, 1944, 114.
[7] Ziegler and Wilms, *Annalen*, 1950, **567**, 1; Cope, Pike, and Spencer, *J. Amer. Chem. Soc.*, 1953, **75**, 3212.
[8] Domnin, *J. Gen. Chem.* (*U.S.S.R.*), 1938, **8**, 851.
[9] Cope, Burg, and Fenton, *J. Amer. Chem. Soc.*, 1952, **74**, 173.
[10] Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890.
[11] Cope and Marshall, *J. Amer. Chem. Soc.*, 1953, **75**, 3208.

gave 3-benzylidene*cyclo*octene (V). The incomplete isomerisation of the alcohol (II) indicates that in the *cyclo*octene series, in contrast to the smaller rings, the double bond has considerable stability in the endocyclic position; in this connection it is interesting that Kistiakowsky [12] and Lister,[13] from studies on the hydrogenation and bromination in the series *cyclo*pentene to *cyclo*octene, have concluded that *cyclo*octene is the most stable and least reactive of these *cyclo*olefins.



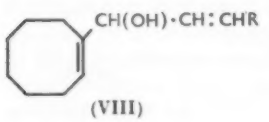
(I) (II) (III) (V) (VI) (VII) (IV)

Interaction of *cyclo*octenyl-lithium with benzophenone gave the alcohol (VI) but the acid rearrangement of this was accompanied by dehydration to 3-diphenylmethylene-*cyclo*octene (VII).

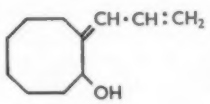
For the diallylic alcohols (VIII; R = H or Me), which were readily prepared by reaction with acraldehyde and crotonaldehyde respectively, two directions of rearrangement are possible. In the five-, six-, and seven-membered ring series [1,2,4] only one isomer was obtained in each case, though the migration took opposite courses according to whether R was H or Me. In the present investigation 1-*cyclo*oct-1′-enylallyl alcohol (VIII; R = H) gave 2-allylidene*cyclo*octanol (IX), the structure of which was established by oxidation to 2-allylidene*cyclo*octanone and by catalytic hydrogenation to 2-*n*-propyl*cyclo*octanol. The latter was converted into 2-*n*-propyl*cyclo*octanone and an authentic specimen, characterised by a 2 : 4-dinitrophenylhydrazone, was prepared by ring-expansion of *cyclo*heptanone with *N*-*n*-butyl-*N*-nitrosourethane in methanol; the immediate product of this reaction appears to be the unusually stable hemiketal (XI), hydrolysis of which required heating with sulphuric acid. The direction of rearrangement of the alcohol (VIII; R = H) is thus the same as for the analogous compounds with smaller rings. 1-*cyclo*Oct-1′-enylbut-2-en-1-ol (VIII; R = Me) (from which, by oxidation, the corresponding ketone was prepared) on rearrangement gave a mixture of a butenol and a dehydration product. By analogy with the direction of migration in the smaller-ring systems, the butenol is probably (X); this structure is supported by the infrared spectrum, which showed a band at 1363 cm.$^{-1}$ characteristic of a methyl group in a >CMe·OH environment, with only a very weak band at 1374 cm.$^{-1}$, the position characteristic of a −CMe= group. The butenol was oxidised by manganese dioxide to (probably) 4-*cyclo*oct-1′-enylbut-3-en-2-one (XII) characterised by a semicarbazone, which exhibited high-intensity ultraviolet light absorption ($\lambda_{max.}$ 2940 and 3030 Å; ε 42,000 and 36,000) typical of a dienone derivative. Dehydration of the mixture gave a conjugated triene, the infrared absorption spectrum of which showed maxima at 895 (vinyl group) and 1377 cm.$^{-1}$ (methyl group); the absorption intensities showed that the vinyl structure (XIII) was present in smaller amount than the isomer (XIV). If the proposed structure (X) for the rearranged alcohol is correct, dehydration is evidently accompanied by further rearrangement.

[12] Kistiakowsky, Conn, and Smith, *ibid.*, 1939, **61**, 1868.
[13] Lister, *ibid.*, 1941, **63**, 143.

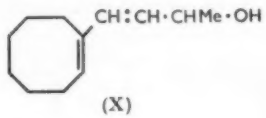
In the reactions of *cyclo*octenyl-lithium with carbon dioxide and with carbonyl compounds, *cyclo*octene was usually isolated as a by-product. Cross-metallation of the solvent ether is well known [14] with lithium alkyls and with benzylic lithium derivatives, and results in formation of the parent alkane, but hitherto it has not been reported to occur with



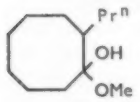
(VIII)



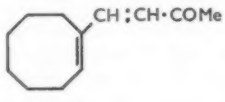
(IX)



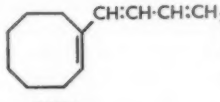
(X)



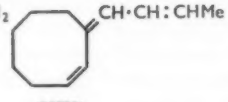
(XI)



(XII)



(XIII)



(XIV)

lithium alkenyls. Investigation has now shown,[15] however, that this appears to be of general occurrence with *cyclo*alkenyl-lithium preparations.

Experimental

Analytical data were determined in the organic microanalytical (Mr. F. H. Oliver, Miss J. Cuckney, and staff) and spectroanalytical (Mr. R. L. Erskine and Mrs. A. I. Boston) laboratories of this Department. The *cyclo*octatetraene was kindly made for us by British Oxygen Research and Development Ltd., by the polymerisation of acetylene under pressure.

cyclo*Octanone and* cyclo*Nonanone*.—(*a*) In accord with directions of Kohler *et al.*,[5] methylnitrosourethane (105 g.) was added to *cyclo*heptanone (56 g.), methanol (52 ml.) and powdered anhydrous sodium carbonate (1 g.). The mixture was kept overnight, filtered, and fractionated, giving: (i) low-boiling products (10 g.), b. p. 75—117°/100 mm.; (ii) impure *cyclo*octanone (25 g.), b. p. 118—127°/100 mm.; (iii) *cyclo*octanone (15 g.), b. p. 128—130°/100 mm., which solidified (m. p. 31°) and formed a 2 : 4-dinitrophenylhydrazone, yellow needles (from ethyl acetate–methanol), m. p. 167°, $\lambda_{max.}$ 3680 Å (ε 24,000) in $CHCl_3$ (Found: N, 18·3. Calc. for $C_{14}H_{18}O_4N_4$: N, 18·3%) (Brady [16] gives m. p. 163°); (iv) impure *cyclo*nonanone (5 g.), b. p. 131—135°/100 mm. The 2 : 4-*dinitrophenylhydrazone* of *cyclo*nonanone crystallised from ethyl acetate–methanol in yellow needles, m. p. 168°, $\lambda_{max.}$ 3680 Å (ε 25,000) in $CHCl_3$ (Found: C, 56·2; H, 6·3; N, 17·3. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·3; N, 17·5%).

2-*Benzylidene*cyclo*nonanone*, prepared from the ketone (4 g.) and benzaldehyde (3·2 g.) in aqueous ethanol–0·1M-potassium hydroxide (20 ml.) at room temperature, had b. p. 90° (bath)/10^{-5} mm., n_D^{25} 1·5792, $\lambda_{max.}$ 2700 (ε 16,000) and 2800 Å (ε 13,500) in hexane (Found: C, 84·1; H, 9·0. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%), and formed a red 2 : 4-*dinitrophenylhydrazone* which after chromatography in benzene on alumina and crystallisation from ethyl acetate–methanol had m. p. 158°, $\lambda_{max.}$ 3940 Å (ε 25,000) in $CHCl_3$ (Found: C, 64·7; H, 6·0; N, 13·7. $C_{22}H_{24}O_4N_4$ requires C, 64·7; H, 5·9; N, 13·7%).

(*b*) Methylnitrosourea (230 g.) was added in small portions during 8 hr. to a stirred solution of potassium hydroxide (130 g.) in water (130 ml.) and methanol (600 ml.) containing *cyclo*heptanone (220 g.), at 5—10° (cooling). The mixture was stirred for 12 hr. at room temperature and then neutralised with acetic acid (35 ml.). The inorganic salts were filtered off and washed with methanol (50 ml.). The filtrate and washings were combined, and most of the methanol was removed by distillation through an 8 in. Dufton column. The residual solution was diluted with water (500 ml.), the aqueous layer extracted with ether (3 × 200 ml.), and the

[14] Haubein, *Iowa State Coll. J. Sci.*, 1943, **18**, 48; *Chem. Abs.*, 1944, **38**, 716; Ziegler and Gellert, *Annalen*, 1950, **567**, 185; Braude, Chapter 4 in "Progress in Organic Chemistry," J. W. Cook, Ed., Vol. III, Butterworths, London, 1955.

[15] Houghton and Waight, unpublished observations.

[16] Brady, *J.*, 1931, 756.

extract added to the organic layer. The combined organic material was dried ($MgSO_4$) and carefully fractionated through a 2′ Stedman column, giving: (i) low-boiling material (98 g.), b. p. 82—98°/28 mm., n_D^{21} 1·4570—1·4650; (ii) impure *cyclo*octanone (28 g.), b. p. 98—101°/28 mm., m. p. 21—35°; (iii) a series of fractions of *cyclo*octanone (82 g., 32%), b. p. 101°/28 mm., m. p.s 38—41° to 42—43·5° (Kohler *et al.*[5] give m. p. 43·8°). Gas–liquid chromatography of the material of m. p. 42—43·5° showed it to be at least 99% pure.

cyclo*Octene*.—(*a*) *cyclo*Octanone (15·4 g.) was reduced with lithium aluminium hydride (2 g.) in boiling ether (250 ml.), the mixture was treated with water and ice-cold 10% sulphuric acid (150 ml.), and the crude *cyclo*octanol was isolated with ether and dehydrated by distillation from naphthalene-β-sulphonic acid at 180—250°, giving *cis-cyclo*octene (10 g.), b. p. 140°/760 mm., n_D^{21} 1·4690 (Kohler *et al.*[5] give b. p. 144°/773 mm., n_D^{20} 1·4693).

(*b*) *cis-cis-cyclo*Octa-1 : 5-diene (79 g.), kindly supplied by Dr. H. W. B. Reed [17] (Imperial Chemical Industries Limited, Billingham), was hydrogenated in ether (400 ml.) in the presence of 5% palladium–charcoal (0·9 g.). The rapid uptake of gas ceased after 17·8 l. of hydrogen at 18°/804 mm. (calc. for 1 mol., 16·5 l.) had been absorbed. The catalyst was filtered off and the solution was fractionated, giving *cis-cyclo*octene (72 g.), b. p. 88°/141 mm., n_D^{21} 1·4690.

(*c*) *cyclo*Octatetraene (50 g.) in ether (100 ml.) was hydrogenated in the presence of a 1% palladium–calcium carbonate catalyst (1 g.) at room temperature.[18] When the uptake of hydrogen had ceased, the catalyst was filtered off and the solution was fractionated, giving *cis-cyclo*octene (45 g.), b. p. 140°/760 mm., n_D^{21} 1·4690.

The infrared spectra (3—15 μ) of all three samples were indistinguishable and exhibited $\nu_{max.}$ 3000(w) (=C–H stretching), 2890 (s) and 2820 (s) (>C–H stretching), 1645 (w) (C=C stretching), 1460 (s) (>C–H bending), 1355 (w), 1246 (w), 982 (w), 890 (m), 752 (s), and 700 (m) $cm.^{-1}$, in excellent agreement with Cope *et al.*[7]

1-*Chloro*cyclo*octene*.—(a) (" *Kohler's chloride.*") Liquid chlorine (13 ml.) was allowed to boil in a stream of nitrogen, and the gas was passed into a solution of *cyclo*octene (22 g.; freshly distilled from sodium) in peroxide-free chloroform (50 ml.) at −60°. Distillation gave 1 : 2-di-chloro*cyclo*octane (26·4 g.), b. p. 74°/1 mm., n_D^{24} 1·5055 (Kohler *et al.*[5] give b. p. 130·5°/25 mm., n_D^{20} 1·5061). When chlorine was passed into a solution of *cyclo*octene in commercial chloroform, a mixture, b. p. 86—120°/0·5 mm., n_D^{20} 1·511—1·542, was obtained from which a fraction corresponding to 1 : 2 : 3-*trichloro*cyclo*octane*, b. p. 100—103°/0·5 mm., n_D^{20} 1·5305 (Found: Cl, 48·7. $C_8H_{13}Cl_3$ requires Cl, 49·4%), was isolated.

1 : 2-Dichloro*cyclo*octane (26 g.), benzene (60 ml.), and dimethylamine (30 ml.) were heated in a sealed vessel at 160° for 15 hr. After cooling, dimethylamine hydrochloride (10·3 g.) was filtered off and the filtrate was washed with dilute hydrochloric acid, dried (Na_2SO_4), and distilled, giving *cis*-1-chloro*cyclo*octene (13 g.), b. p. 68°/13 mm., n_D^{21} 1·4923 (Kohler *et al.*[5] give b. p. 77—78°/19 mm., n_D^{20} 1·4928). The infrared spectrum showed $\nu_{max.}$ 3030 (w) (=C–H stretching) 2890 and 2850 (s) (>C–H stretching), 1665 (s) (C=C stretching), 1468 (s), 1449 (s) and 1360 (m), (>C–H bending), 1220 (m), 1125 (s), 1000 (m), 896 (s), 840 (s), 775 (m), and 739 (m) $cm.^{-1}$.

(b) (" *Domnin's chloride.*") *cyclo*Octanone (26·9 g.), m. p. <38°, in light petroleum (30 ml.; b. p. 40—60°) was added during 20 min. to a stirred suspension of phosphorus pentachloride (65 g.) in light petroleum (20 ml.; b. p. 40—60°). The mixture was stirred for 2 hr., then poured into cold water (500 ml.), and the organic material extracted with ether (2 × 100 ml.). The extract was dried ($MgSO_4$) and fractionated through an 8 in. Dufton column, giving 1-chloro-*cyclo*octene (13·4 g., 44%), b. p. 82—86°/21 mm., n_D^{20} 1·4918 (Domnin [8] gives b. p. 64—68°/10 mm.). The infrared spectrum was identical with that of " Kohler's chloride."

1-*Bromo*cyclo*octene*.—By following the procedure of Kohler *et al.*,[5] *cyclo*octene (11 g.) was converted into 1-bromo*cyclo*octene (10·5 g.), b. p. 88—90°/15 mm., n_D^{20} 1·5178 (Kohler *et al.*[5] give b. p. 97—98°/23 mm., n_D^{20} 1·5182). The infrared spectrum showed $\nu_{max.}$ 2900 (s) (>C–H stretching), 1640 (m) (C=C stretching), 1450 (s) and 1355 (m) (>C–H bending), 1212 (s), 1107 (m), 1010 (m), 981 (m), 898 (m), 868 (s), 830 (s), 771 (m), and 730 (m) $cm.^{-1}$.

cyclo*Octene*-1-*carboxylic Acid*.—(*a*) 1-Bromo*cyclo*octene (7·2 g.) in ether (15 ml.) was added to a stirred suspension of finely cut lithium (0·57 g.) in dry ether (100 ml.) under nitrogen. The solution became turbid within 2 min., and after about 5 min. the ether was refluxing. Reaction was complete after 2 hr. and solid carbon dioxide (300 g.) was then added. When the mixture

[17] Reed, *J.*, 1954, 1931.
[18] Cf. Reppe, Schlichting, Klager, and Toepel, *Annalen*, 1948, **560**, 1; Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128.

had attained room temperature, water (75 ml.) was added and the mixture was acidified with hydrochloric acid. The ether layer was separated and extracted with saturated aqueous sodium hydrogen carbonate. Acidifying this extract with concentrated hydrochloric acid precipitated *cyclo*octene-1-carboxylic acid (0·99 g., 17%); it was recrystallised from water and sublimed at 10^{-4} mm. and then had m. p. 102—103°, $\lambda_{max.}$ 2150 Å (ε 12,000) in EtOH (Found: C, 69·9; H, 9·3. Calc. for $C_9H_{14}O_2$: C, 70·1; H, 9·2%) (Cope *et al.*[9] give m. p. 101·8—102·6°). The *amide*, prepared by treatment with thionyl chloride followed by ammonia, crystallised from water as plates, m. p. 106° (Found: C, 70·6; H, 10·0; N, 9·0. $C_9H_{15}ON$ requires C, 70·55; H, 9·9; N, 9·1%).

(*b*) 1-Chloro*cyclo*octene (18·5 g.) was added to a stirred suspension of freshly cut lithium (1·8 g.) in ether (350 ml.) under nitrogen. The mixture was stirred and refluxed for 24 hr., assuming an opaque, greenish-grey appearance. Carboxylation as above gave 1-*cyclo*octene-carboxylic acid (3·2 g., 16%), which crystallised from light petroleum (b. p. 40—60°) as plates, m. p. 102°. The ether layer on distillation, gave *cyclo*octene (2·5 g., 19%), b. p. 31°/10 mm., n_D^{23} 1·4680 (Found: C, 87·3; H, 13·0. Calc. for C_8H_{14}: C, 87·2; H, 12·8%), which readily decolorised bromine in chloroform and showed an infrared spectrum indistinguishable from that of an authentic specimen.

1-*Hydroxymethyl*cyclo*octene*.—Gaseous formaldehyde, generated by heating paraformaldehyde (1·5 g.) at 180—200°, was passed into a stirred solution of lithium alkenyl (from 1-bromo-*cyclo*octene, 8·6 g.) in ether under nitrogen at 0°. The solution was kept overnight at room temperature, saturated aqueous ammonium chloride (50 ml.) was added at 0°, and the ether layer was separated, dried (Na_2SO_4), and fractionated, giving 1-*hydroxymethyl*cyclo*octene* (1·6 g., 25%), b. p. 104—105°/9 mm., n_D^{23} 1·4975 (Found: C, 77·4; H, 11·6. $C_9H_{16}O$ requires C, 77·1; H, 11·5%). The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 97—98° (Found: C, 57·3; H, 5·5; N, 8·7. $C_{16}H_{18}O_6N_2$ requires C, 57·5; H, 5·4; N, 8·4%).

1-1′-*Hydroxyethyl*cyclo*octene*.—Acetaldehyde (2·4 g.) in ether (20 ml.) was added dropwise during 10 min. to a solution of *cyclo*octenyl-lithium (from 1-chloro*cyclo*octene, 7·7 g.) in ether (200 ml.). After this had been stirred for 1 hr. at room temperature, saturated aqueous ammonium chloride (100 ml.) was added at 0° and the ether layer was separated, dried ($MgSO_4$), and fractionated, giving: (i) *cyclo*octene (1·14 g., 19%), b. p. 41—42°/16 mm., n_D^{22} 1·4685; (ii) 1-1′-*hydroxyethyl*cyclo*octene* (4·57 g., 55%), b. p. 72—79°/0·9 mm., n_D^{21} 1·4978 (Found: C, 77·5; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%), whose 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 53—54° (Found: C, 58·8; H, 6·0; N, 8·1. $C_{17}H_{20}O_6N_2$ requires C, 58·6; H, 5·8; N, 8·0%).

1-*Acetyl*cyclo*octene*.—A solution of the foregoing alcohol (3·14 g.) in pyridine (30 ml.) was added to chromium trioxide (3·5 g.) in pyridine (35 ml.) at 0° and the mixture was then kept at room temperature for 3 hr. The dark brown solution was carefully diluted with water (150 ml.) and then extracted with ether (3 × 50 ml.). The ether extracts were dried (Na_2SO_4) and distilled, giving the crude ketone (2·8 g.), b. p. 100°/11 mm., n_D^{21} 1·4991; this was converted into the *semicarbazone* (1·53 g., 40%) which after crystallisation from ethanol and sublimation at 10^{-4} mm. had m. p. 191—192°, $\lambda_{max.}$ 2650 Å (ε 20,500) in EtOH (Found: C, 63·2; H, 9·2; N, 20·3. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·15; N, 20·1%). Steam-distillation of the semicarbazone with twice its weight of phthalic anhydride regenerated almost quantitatively pure 1-*acetyl*cyclo*octene*, b. p. 62—64°/0·5 mm., n_D^{20} 1·4998, $\lambda_{max.}$ 2360 Å (ε 11,400) in EtOH (Found: C, 78·2; H, 10·6. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%). The infrared spectrum showed $\nu_{max.}$ 1667 (s) (C=O stretching) and 1637 cm.$^{-1}$ (m) (C=C stretching). The ketone formed a red 2 : 4-*dinitrophenylhydrazone* which after chromatography in benzene on alumina and crystallisation from ethyl acetate had m. p. 165°, $\lambda_{max.}$ 3850 Å (ε 26,000) in $CHCl_3$ (Found: C, 57·7; H, 6·1; N, 16·7. $C_{16}H_{20}O_4N_4$ requires C, 57·8; H, 6·1; N, 16·9%).

The ketone (0·57 g.) was hydrogenated in ethanol (20 ml.) over 5% palladium–charcoal (0·1 g.), to give acetyl*cyclo*octane (0·51 g., 88%), b. p. 81—83°/2 mm., n_D^{22} 1·4762. The infrared spectrum showed $\nu_{max.}$ 1706 cm.$^{-1}$ (s) (C=O stretching). The semicarbazone after crystallisation from aqueous ethanol and sublimation at 10^{-4} mm. had m. p. 180—181° (lit.,[10] 180—181°) (Found: C, 62·5; H, 10·1; N, 19·6. Calc. for $C_{11}H_{21}ON_3$: C, 62·5; H, 10·0; N, 19·9%).

α-(cyclo*Oct*-1-*enyl*)*benzyl Alcohol*.—Freshly distilled benzaldehyde (6·4 g.) in ether (30 ml.) was added dropwise to a solution of *cyclo*octenyl-lithium (from 1-chloro*cyclo*octene, 8·7 g.) at

[10] Ruzicka and Boekenoogen, *Helv. Chim. Acta*, 1931, **14**, 1319.

such a rate that the ether refluxed gently. Stirring was continued for 2 hr. at room temperature. Saturated aqueous ammonium chloride (300 ml.) was then added at 0°, and the ether layer was separated, dried ($MgSO_4$), and distilled, giving (i) *cyclo*octene (1·47 g., 22%), b. p. 32—38°/12 mm., n_D^{20} 1·4755, and (ii) α-(cyclo*oct*-1-*enyl*)*benzyl alcohol* (6·7 g., 51%), b. p. 111—112°/0·01 mm., n_D^{21} 1·5545, which solidified at 0° and then had m. p. 25—29° (Found: C, 83·5; H, 9·45. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). The light absorption in ethanol ($\lambda_{max.}$ 2470 Å; ε 2100) showed that the product probably contained a small amount of ketone, but was free from rearranged alcohol.

cyclo*Oct*-1-*enyl Phenyl Ketone*.—The above alcohol (1·32 g.) in dry benzene (15 ml.) was added to the complex prepared from chromium trioxide (1·5 g.) and pyridine (15 ml.), and the mixture was shaken for 12 hr. at room temperature. The solid was filtered off and washed with benzene (20 ml.). The filtrate and washings were combined and passed through a short alumina column (Spence H). The column was eluted with benzene (50 ml.), to give the ketone (1·16 g., 89%) b. p. 128—132°/0·8 mm., n_D^{23} 1·5604 (Cope and Marshall [11] give b. p. 94°/0·06 mm., n_D^{25} 1·5630); the infrared spectrum showed $\nu_{max.}$ 1641 cm.$^{-1}$ (s) (C=O stretching); the light absorption max. in EtOH was at 2450 Å (ε 11,800). The ketone formed a red 2 : 4-dinitrophenylhydrazone which crystallised from methanol–ethyl acetate in two forms, m. p. 135—138° and m. p. 160—161° (Cope and Marshall [11] give m. p. 161—162°).

Oxotropic Rearrangement of α-(cyclo*Oct*-1-*enyl*)*benzyl Alcohol*.—A solution of the alcohol (1·67 g.) in a 0·1M-solution of hydrogen chloride in 80% aqueous acetone (40 ml.) was kept for 18 hr. at room temperature, then neutralised with saturated aqueous sodium hydrogen carbonate, and the acetone was removed under reduced pressure. The organic material was extracted with ether (2 × 10 ml.), and the extract was dried ($MgSO_4$) and distilled, giving a product (1·34 g., 80%), b. p. 130—132°/0·5 mm., n_D^{23} 1·5554, $\lambda_{max.}$ 2500 Å (ε 5500) in EtOH. Re-treatment of the product (0·79 g.) for a further 85 hr. gave material (0·56 g., 71%), b. p. 128—135°/0·5 mm., n_D^{22} 1·5655, $\lambda_{max.}$ 2500 Å (ε 8000) in EtOH.

A mixture of the rearrangement products (0·83 g.) in dry benzene (15 ml.) was added to the complex prepared from chromium trioxide (1·0 g.) and pyridine (10 ml.) in benzene (10 ml.), and shaken for 12 hr. at room temperature, to yield a product (0·69 g., 84%), b. p. 133—138°/0·9 mm., n_D^{21} 1·5668, $\lambda_{max.}$ 2500 and 2830 Å (ε 12,500 and 6,850 respectively) in EtOH, indicating the presence of the two corresponding ketones.

2-*Benzylidene*cyclo*octanone*.—(*a*) A mixture of *cyclo*octanone (14·0 g.), benzaldehyde (7·5 g.), potassium hydroxide (2·5 g.), and water (65 ml.) was refluxed for 3½ hr., then cooled, acidified with acetic acid (3·5 ml.) in water (100 ml.), and extracted with ether (2 × 50 ml.). The extract was dried ($MgSO_4$) and distilled, giving 2-*benzylidene*cyclo*octanone* (8·37 g., 35%), b. p. 145—150°/0·8 mm., n_D^{22} 1·5780, which solidified when cooled in ice, and after recrystallisation from hexane had m. p. 76—77°, $\lambda_{max.}$ 2760 Å (ε 11,600) in *cyclo*hexane, $\lambda_{max.}$ 2850 Å (ε 15,800) in EtOH (Found: C, 84·3; H, 8·5. $C_{15}H_{18}O$ requires C, 84·1; H, 8·5%). The 2 : 4-*dinitrophenylhydrazone*, after chromatography in benzene on alumina and crystallisation from ethyl acetate–methanol, had m. p. 181—182°, $\lambda_{max.}$ 3900 Å (ε 25,000) in $CHCl_3$ (Found: C, 63·8; H, 5·9; N, 13·7. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%).

(*b*) Benzaldehyde (3·0 g.) in 50% aqueous ethanol (30 ml.) was added with vigorous stirring to *cyclo*octanone (15·1 g.) in 50% aqueous ethanol–0·1M-potassium hydroxide (200 ml.). After 4 hr., water (300 ml.) was added and the solution was extracted with ether. The ether extract was dried (Na_2SO_4) and distilled, giving some unchanged benzaldehyde and *cyclo*octanone, followed by a fraction (1·6 g.), b. p. 142°/0·3 mm., which was redistilled to give 2-(α-*hydroxybenzyl*)cyclo*octanone*, b. p. 80°/10^{-5} mm., n_D^{20} 1·5480 [Found: C, 77·4; H, 8·5; active hydrogen (Zerewitinoff), 0·43. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7; 1H, 0·43%].

The hydroxy-ketone (1·1 g.) was heated with naphthalene-β-sulphonic acid (50 mg.) at 70°/10^{-4} mm. 2-Benzylidene*cyclo*octanone (0·6 g.) sublimed and after crystallisation from light petroleum (b. p. 40—60°) had m. p. 76—77°.

2-*Benzylidene*cyclo*octanol*.—Lithium aluminium hydride (0·15 g.) in ether (50 ml.) was added dropwise during 10 min. to 2-benzylidene*cyclo*octanone (2·0 g.) in ether (30 ml.) at 0°. After a further 10 minutes' stirring at 0°, saturated aqueous ammonium chloride (100 ml.) was added. The ether layer was separated, dried ($MgSO_4$), and distilled, giving the *alcohol* (1·80 g., 89%), b. p. 140—143°/0·5 mm., n_D^{24} 1·5770, $\lambda_{max.}$ 2500 Å (ε 12,500) in EtOH (Found: C, 83·15; H, 9·25. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). Distillation of the alcohol (0·71 g.) from

naphthalene-β-sulphonic acid (0·5 g.) gave 3-*benzylidene*cyclo*octene* (0·45 g., 68%), b. p. 60° (bath)/10^{-5} mm., n_D^{21} 1·5962, $\lambda_{max.}$ 2260, 2510, 2700, and 2800 Å (ε 9000, 10,000, 14,000, and 14,000 respectively) in EtOH (Found: C, 90·0; H, 9·2. $C_{15}H_{18}$ requires C, 90·85; H, 9·15%).

Oxotropic Rearrangement of 2-*Benzylidene*cyclo*octanol*.—A solution of the alcohol (0·59 g.) in a 0·1M-solution of hydrogen chloride in 80% aqueous acetone (20 ml.) was kept for 63 hr. at room temperature. Isolation in the usual way gave a product (0·39 g., 66%), b. p. 138°/0·9 mm., n_D^{23} 1·5710, $\lambda_{max.}$ 2510 Å (ε 8200) in EtOH. The infrared spectrum was almost indistinguishable from that of the material obtained by oxotropic rearrangement of α-(*cyclo*oct-1-enyl)-benzyl alcohol.

α-(cyclo*Oct*-1-*enyl*)*diphenylmethanol*.—Benzophenone (4·5 g.) in ether (40 ml.) was added to the lithium alkenyl (from 1-bromo*cyclo*octene, 4·7 g.) in ether at room temperature. Next day, saturated aqueous ammonium chloride (50 ml.) was added, and the ether layer was separated, dried (Na_2SO_4–K_2CO_3), and distilled, giving the *alcohol* (4·0 g., 55%), b. p. 80—90° (bath)/10^{-5} mm., n_D^{23} 1·5925 (Found: C, 86·3; H, 8·3. $C_{21}H_{24}O$ requires C, 86·25; H, 8·3%).

A solution of the alcohol (3·3 g.) in 80% aqueous acetone–0·1M-hydrogen chloride (100 ml.) was kept for 3 days at room temperature. The mixture was neutralised with potassium carbonate and worked up by the procedure previously described, yielding a product (2·5 g.), b. p. 70—80° (bath)/10^{-5} mm., n_D^{21} 1·607—1·615 (Found: C, 89·9; H, 8·1%), which was redistilled from naphthalene-β-sulphonic acid (50 mg.) to give 3-*diphenylmethylene*cyclo*octene*, b. p. 100° (bath)/10^{-3} mm., n_D^{20} 1·6192, $\lambda_{max.}$ 2260, 2510, 2560, and 2670 Å (ε 21,500, 10,000, 11,500, and 11,500, respectively) in EtOH (Found: C, 91·8; H, 8·1. $C_{21}H_{22}$ requires C, 91·9; H, 8·1%).

1-cyclo*Oct*-1′-*enylallyl alcohol*.—Freshly distilled acraldehyde (4·4 ml.) in ether (15 ml.) was added to 1-*cyclo*octenyl-lithium (from 1-bromo*cyclo*octene, 12·9 g.) in ether at 0°. After 1·5 hr. at room temperature, saturated aqueous ammonium chloride (50 ml.) was added at 0° and the ether layer was separated, dried (Na_2SO_4–K_2CO_3), and distilled, giving the *alcohol* (7·0 g., 62%), b. p. 72—74°/0·15 mm., n_D^{23} 1·5080, $\varepsilon < 1000$ between 2000 and 3000 Å (Found: C, 79·4; H, 11·1. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%).

2-*Allylidene*cyclo*octanol*.—A solution of the foregoing alcohol (7·5 g.) in 80% aqueous acetone–0·05M-hydrogen chloride (200 ml.) was kept for 15 hr. at room temperature and then neutralised with potassium carbonate. The acetone was distilled off through a column, and the product was isolated by ether-extraction, giving the *alcohol* (5·1 g.), b. p. 80—82°/0·5 mm., n_D^{24} 1·5335, $\lambda_{max.}$ 2380 Å (ε 22,000) in EtOH (Found: C, 79·6; H, 11·0. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%).

2-*Allylidene*cyclo*octanone*.—The foregoing alcohol (1·5 g.) in pyridine (20 ml.) was added to chromium trioxide (2·0 g.) in pyridine (20 ml.) at 0°. The mixture was kept overnight at room temperature and diluted with water (200 ml.), and the product, which gave no colour with Schiff's reagent, was isolated by ether-extraction and distilled, giving the *ketone* (1·1 g.), b. p. 76—78°/0·5 mm., n_D^{18} 1·5508, $\lambda_{max.}$ 2800 Å (ε 16,000) in EtOH (Found: C, 80·5; H, 9·9. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). The 2 : 4-*dinitrophenylhydrazone*, after chromatography in benzene on alumina and crystallisation from ethyl acetate–methanol, had m. p. 225°, $\lambda_{max.}$ 3930 Å (ε 32,000) in $CHCl_3$ (Found: C, 59·3; H, 6·1; N, 16·1. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·85; N, 16·3%).

2-n-*Propyl*cyclo*octanol*.—2-Allylidene*cyclo*octanol (1·63 g.) was hydrogenated in methanol (25 ml.) over platinic oxide (25 mg.). The uptake of hydrogen ceased when 490 ml. at 20°/782 mm. (calc. for 2 mol., 468 ml.) had been absorbed. The catalyst was filtered off and the solution distilled, giving the *alcohol* (0·5 g.), b. p. 70—72°/0·5 mm., n_D^{20} 1·4770 (Found: C, 78·0; H, 12·9. $C_{11}H_{22}O$ requires C, 77·6; H, 13·0%). The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 60—80°) and had m. p. 78—79° (Found: C, 59·6; H, 7·0; N, 7·7. $C_{18}H_{24}O_6N_2$ requires C, 59·3; H, 6·6; N, 7·7%).

2-n-*Propyl*cyclo*octanone*.—(*a*) The foregoing alcohol (0·3 g.) was oxidised with chromic oxide (0·5 g.) in pyridine (10 ml.), and the product was treated with Brady's reagent, giving 2-*n*-propyl*cyclo*octanone 2 : 4-dinitrophenylhydrazone (0·5 g.) which, after chromatography in benzene on alumina and crystallisation from methanol, had m. p. 133—134°, undepressed on admixture with the specimen described below.

(*b*) *N*-*n*-Butyl-*N*-nitrosourethane [20] (5 g.) was added to a stirred mixture of *cyclo*heptanone

[20] Wilds and Meader, *J. Org. Chem.*, 1948, **13**, 763; cf. Cook, Raphael, and Scott, *J.*, 1951, 695.

(18·5 ml.), methanol (17 ml.), and sodium carbonate (0·3 g.). After 30 min., a vigorous reaction took place which was controlled by external cooling. More urethane (total 26 g.) was then added in portions during 1 hr. at 20—25°. The mixture was kept overnight and filtered, and the solution was fractionated, giving a product formulated as 1-*methoxy*-2-n-*propyl*cyclo*octan*-1-*ol* (7 g.), b. p. 41°/0·5 mm., n_D^{23} 1·4571 (Found: C, 71·95; H, 11·9. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·1%).

The hemiketal (2 g.) was heated with acetic acid (20 ml.) and sulphuric acid (2 g.) for 3 hr. at 80°. The solution was kept for 3 days at room temperature, diluted with water, neutralised with sodium carbonate, and extracted with ether. The ether extract was dried (Na_2SO_4) and distilled, giving 2-n-*propyl*cyclo*octanone* (0·7 g.), b. p. 69°/0·1 mm., n_D^{21} 1·4590 (Found: C, 78·5; H, 12·0. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). The 2 : 4-*dinitrophenylhydrazone*, obtained by treating either the hemiketal or the ketone with Brady's reagent, was chromatographed in benzene–chloroform on alumina and crystallised from ethyl acetate in fine orange needles, m. p. 132°, $\lambda_{max.}$ 3700 Å (ε 27,000) in $CHCl_3$ (Found: C, 58·5; H, 7·1; N, 16·0. $C_{17}H_{24}O_4N_4$ requires C, 58·6; H, 6·9; N, 16·1%).

1-cyclo*Oct*-1′-*enylbut*-2-*en*-1-*ol*.—Crotonaldehyde (2·4 ml.) in ether (20 ml.) was added dropwise during 10 min. to a solution of *cyclo*octenyl-lithium (from 1-chloro*cyclo*octene, 4·4 g.) in ether (150 ml.). After 2 hours' stirring at room temperature, saturated aqueous ammonium chloride (100 ml.) was added at 0°. The ether layer was separated, dried ($MgSO_4$), and fractionated, giving *cyclo*octene (0·80 g., 24%), b. p. 30—31°/10 mm., n_D^{22} 1·4660, and the *alcohol* (2·51 g., 46%), b. p. 90—94°/0·4 mm., n_D^{22} 1·5075 (Found: C, 80·2; H, 11·3. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%), $\varepsilon < 800$ between 2000 and 3000 Å in EtOH.

1-cyclo*Oct*-1′-*enylbut*-2-*en*-1-*one*.—The above alcohol (1·21 g.) in dry benzene (10 ml.) was shaken with the complex prepared from chromium trioxide (1·4 g.) and pyridine (15 ml.) in benzene (15 ml.) for 3 hr. at room temperature. Isolation of the organic material as above gave the ketone (0·91 g., 76%), b. p. 105—107°/1·5 mm., n_D^{21} 1·5205, $\lambda_{max.}$ 2450 Å (ε 7100) in EtOH, $\nu_{max.}$ 1660 (s), 1616 (s), and 975 (s) cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate and had m. p. 233—234°, $\lambda_{max.}$ 3980 Å (ε 27,600) (Found: C, 60·6; H, 6·1; N, 15·4. $C_{18}H_{22}O_4N_4$ requires C, 60·3; H, 6·2; N, 15·6%).

Rearrangement of 1-cyclo*Oct*-1′-*enylbut*-2-*en*-1-*ol*.—A solution of the alcohol (0·99 g.) in a 0·1M-solution of hydrogen chloride in 80% aqueous acetone (25 ml.) was kept for 24 hr. at room temperature. Isolation of the product in the usual way gave an oil (0·50 g.), b. p. 80—100°/0·4 mm., n_D^{21} 1·5321, $\lambda_{max.}$ 2400, 2680, and 2770 Å (ε 16,200, 6320, and 6480 respectively) in EtOH, $\nu_{max.}$ 3356 (m) (O–H stretching), 1374 (w) and 1363 (m) (C–H deformation of C–CH_3) and 893 cm.$^{-1}$ (w) (C–H out of plane deformation of C=CH_2).

The above mixture (0·32 g.) was distilled from anhydrous potassium hydrogen sulphate (0·1 g.) to give a product (0·14 g., 49%), b. p. 130—150° (bath)/1·5 mm., n_D^{22} 1·5572 $\lambda_{max.}$ 2680 and 2770 Å (ε 26,100 and 26,300 respectively) in EtOH. The infrared spectrum in CCl_4 shows $\nu_{max.}$ 1377 and 895 cm.$^{-1}$ (ε 29 and 54 respectively).

A further portion of the rearrangement product (2·2 g.) was shaken with manganese dioxide (20 g.) in light petroleum (b. p. 40—60°; 200 ml.) for 3 days, and the product was distilled and treated with semicarbazide acetate and aqueous ethanol, giving (probably) 4-cyclo*oct*-1′-*enylbut*-3-*en*-2-*one semicarbazone* (0·55 g.), which after crystallisation from ethanol and sublimation at 10^{-5} mm. had m. p. 181—182°, $\lambda_{max.}$ 2940 and 3030 Å (ε 42,000 and 36,000 respectively) (Found: C, 66·6; H, 9·2; N, 18·0. $C_{13}H_{21}ON_3$ requires C, 66·4; H, 9·0; N, 17·9%).

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952. *Alkenylation with Lithium Alkenyls. Part XV.* The Formation and Some Reactions of* 1-cyclo*Decenyl-lithium.*

By (the late) E. A. Braude and B. F. Gofton.

1-Chloro*cyclo*decene could not be induced to react with lithium, but 1-bromo*cyclo*decene is readily metallated. 1-*cyclo*Decenyl-lithium undergoes carboxylation to give *cyclo*dec-1-enecarboxylic acid, but reactions with other carbonyl compounds proceed abnormally.

Many of the "non-classical" phenomena associated with "medium-sized" rings are at their height in the *cyclo*decane series [1] and an extension of earlier work [2] to the study of *cyclo*decenyl derivatives was therefore of interest.

The most convenient entry to the *cyclo*decane series is the acyloin condensation of the sebacic esters developed by Prelog and his co-workers.[3] By their procedures, with minor modifications described in the Experimental section, sebacoin can be obtained consistently in 60—65% yields and converted into *cyclo*decanone. Reaction of the latter with phosphorus pentachloride gave 1-chloro*cyclo*decene,[4] but the chloride could not be metallated by lithium under the conditions successfully employed for the lower homologues. A similar lack of reactivity has been observed with other *cyclo*decane derivatives, *e.g.*, in the formation of Grignard reagent from 1-bromo*cyclo*decane,[5] and is probably caused by steric factors which will be accentuated in heterogeneous reactions at metal surfaces.

Attention was next directed to 1-bromo*cyclo*decene, since a markedly greater reactivity of the bromo- over the chloro-*cyclo*alkene was observed in the *cyclo*octene series.[2] *cyclo*-Decanone was reduced to *cyclo*decanol which was dehydrated to a mixture of *cis*- and *trans*-*cyclo*decene,[4,6,7] and this mixture was treated with bromine in chloroform. Unlike the case of *cyclo*octene,[2] appreciable evolution of hydrogen bromide (presumably due to allylic bromine-substitution) was observed and a mixture was obtained from which a solid 1 : 2-dibromo*cyclo*decane was isolated in small yield. Attempts to convert *cyclo*decane-1 : 2-diol into the dibromide by phosphorus tribromide, or by hydrogen bromide in acetic acid, also met with little success; the *cis*-diol gave 1-acetoxy-2-bromo*cyclo*decane while the *trans*-diol did not react.

A method different from that employed for the lower homologues was therefore used. Sebacoin was converted via *cyclo*decanedione into *cyclo*decyne.[3,4] The latter readily added hydrogen bromide, giving the desired 1-bromo*cyclo*decene, which should be the *trans*-ring isomer if the addition proceeds *trans*. In *cyclo*decene itself, the *cis*- and *trans*-ring isomers are of comparable stability, but the relative stability of the *trans*-configuration will, of course, be considerably reduced in 1-substituted derivatives owing to interference between the ring and an "inside" substituent; a model of *trans*-1-bromo*cyclo*decene exhibits appreciable steric strain. The infrared spectra are inconclusive, so that the stereochemistry of the bromide is uncertain though a *cis*-configuration or a mixture of geometrical isomers appears the more likely, particularly in view of the ready conversion into the lithium alkenyl described below.

1-Bromo*cyclo*decene underwent metallation by lithium exothermally and rapidly in ether. Carboxylation gave *cyclo*dec-1-enecarboxylic acid in low yield; the crude product

* Part XIV, preceding paper.

[1] Prelog, *J.*, 1950, 420; Prelog and Schenker, *Helv. Chim. Acta*, 1952, **35**, 2044.
[2] Part XIV, preceding paper.
[3] Prelog *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1741; 1952, **35**, 1598; cf. Brown and Borkowski, *J. Amer. Chem. Soc.*, 1952, **74**, 1894.
[4] Blomquist, Burge, and Suesy, *J. Amer. Chem. Soc.*, 1952, **74**, 3636.
[5] Ruzicka, Barman, and Prelog, *Helv. Chim. Acta*, 1951, **34**, 401.
[6] Cope, McLean, and Nelson, *J. Amer. Chem. Soc.*, 1955, **77**, 1628.
[7] Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1952, 1425; Dreiding and Pratt, *J. Amer. Chem. Soc.*, 1954, **76**, 1902.

had a wide m. p. range (70—115°) possibly indicative of a mixture of isomers, but a single crystallisation gave a sharp-melting acid, m. p. 130—131°, which showed ultraviolet and infrared absorption typical of an αβ-ethylenic acid ($\lambda_{max.}$ 2230 Å, $\nu_{max.}$ 1660 and 1625 cm.$^{-1}$) and was presumably the *cis*-isomer. Its constitution was confirmed by catalytic hydrogenation which afforded *cyclo*decanecarboxylic acid, identical with an authentic specimen [5] kindly provided by Professor V. Prelog.

The reactions of the lithium alkenyl with other carbonyl compounds were abnormal. Thus, with benzaldehyde small and variable yields of material having the composition of the expected alcohol were obtained, but the main product was a hydrocarbon, $C_{20}H_{34}$. This showed no intense ultraviolet absorption above 2100 Å and was not hydrogenated in acetic acid in the presence of platinic oxide, though unsaturation was indicated by rapid reaction with bromine. It seems probable that the hydrocarbon is di(*cyclo*dec-1-enyl), formed by a Wurtz coupling of the lithium alkenyl with unchanged bromide. Analogous side-reactions have also been observed with di- and tri-methylvinyl bromide,[7,8] though not with 1-bromo*cyclo*octene,[2] and it is of interest that di(*cyclo*decyl) is one of the side products in the reactions of *cyclo*decylmagnesium bromide.[5] The resistance of di(*cyclo*decenyl) to catalytic hydrogenation is not unexpected since *cyclo*decene is not reduced under comparable conditions, and the absence of ultraviolet light absorption characteristic of a conjugated system may similarly be ascribed to steric hindrance [9] since models show that the two double bonds cannot be coplanar.

Experimental

Analytical data were determined in the organic microanalytical (Mr. F. H. Oliver and staff) and spectroanalytical (Mr. R. L. Erskine and Mrs. A. I. Boston) laboratories of this Department.

2-*Hydroxy*cyclo*decanone* (*Sebacoin*).—The following procedure, based on the method of Prelog *et al.*,[3] consistently gave yields of 60—65% from dimethyl, diethyl, or dibutyl sebacate. Xylene (2 l.) was distilled into a special, 2 l. round-bottomed flask with a wide (4·5 × 14 cm.) neck fitted with an external water-condenser and a B 45 ground-glass joint. 500 Ml. of xylene were distilled out of the flask, which was heated by an electric mantle, to remove last traces of moisture. Clean sodium pieces (46 g.) were added, and then a stainless-steel head, provided with two side-inlets and a central stirrer running on two internal ball-bearings, driven by a 1/3 h.p. electric motor and fitted with a 1·5 × 13 cm. stainless-steel spiral which scraped the bottom of the flask, was placed in position. A slow stream of oxygen-free nitrogen was passed into the flask and the heating was adjusted so that the xylene refluxed *gently* in the condenser-neck of the flask (if boiling was too vigorous and xylene vapour reached the cone of the steel head, the expansion of the latter cracked the flask). About 1 hr. after correct running conditions had been attained, sebacic ester (1 mol.) in xylene (100 ml.) was added at an even rate during 15 hr. through a finely adjusted dropping funnel. After a further hour's stirring the steel head was replaced by a simple glass head and, while the passage of nitrogen was continued, the flask was cooled in ice–salt, and methanol (10 ml.) was added, followed by 50% sulphuric acid (200 ml.). The sodium sulphate was filtered off and the xylene layer was separated, washed with water, sodium carbonate solution, and again with water, dried (Na_2SO_4), and distilled, giving crude sebacoin (51—55 g.), b. p. 100—110°/1 mm., which solidified and was used without further purification.

cyclo*Decanone*.—Reduction of sebacoin by the method of Prelog *et al.* was found to be highly dependent on the batch of zinc powder used, as has been noted by others.[3,4] Effective batches were selected by carrying out small-scale experiments and estimating the *cyclo*decanone as semicarbazone. The following procedure was used. Sieved zinc powder (11·6 g.) followed by concentrated hydrochloric acid (6·6 g.) was added, with vigorous stirring, to a solution of sebacoin (4·6 g.) in acetic acid (11·6 ml.) in a 250 ml. flask. The mixture was heated to 130° and two further portions of hydrochloric acid (6·6 ml.) were added at intervals of 30 min. The solution was decanted from unchanged zinc, diluted with water (100 ml.), and extracted with ether. The ether extract was washed with sodium carbonate and the solvent was distilled off.

[8] Braude and Evans, *J.*, 1955, 3331.
[9] Cf. Braude, *Experientia*, 1955, **11**, 457.

The residue was treated with aqueous semicarbazide acetate, giving *cyclo*decanone semicarbazone (3·6 g., 56%), m. p. 200°. The ketone, b. p. 103—104°/10 mm., n_D^{18} 1·4825, was regenerated by steam-distillation of the semicarbazone with twice its weight of phthalic anhydride.

A solution of the ketone (4·6 g.) and benzaldehyde (3·2 g.) in aqueous ethanol–1M-potassium hydroxide (20 ml.) was kept at room temperature for 24 hr. The product was isolated with ether and distilled from naphthalene-β-sulphonic acid, giving: (i) 2-*benzylidene*cyclo*decanone* (1·0 g.), b. p. 70°/10^{-4} mm., n_D^{23} 1·5780 (Found: C, 84·3; H, 9·3. $C_{17}H_{22}O$ requires C, 84·25; H, 9·15%), characterised by a red 2 : 4-*dinitrophenylhydrazone* which after chromatography in benzene on alumina and crystallisation from methanol–ethyl acetate had m. p. 143—144° (Found: C, 65·5; H, 6·4; N, 13·3. $C_{23}H_{26}O_4N_4$ requires C, 65·4; H, 6·2; N, 13·3%); (ii) 2 : 10-*dibenzylidene*cyclo*decanone* (80 mg.) which after crystallisation from pentane had m. p. 150—151° (Found: C, 86·9; H, 8·1. $C_{24}H_{26}O$ requires C, 87·2; H, 7·9%). The monobenzylidene derivative is semisolid at room temperature and appears to be a mixture of *cis*- and *trans*-isomers; when melted by warming to 25°, it had $\lambda_{max.}$ 2700 and 2800 Å (ε 21,000 and 18,000 respectively) in hexane, while if completely solidified by cooling below 15° it had $\lambda_{max.}$ 2700 and 2800 Å (ε 9500 and 7000 respectively) in hexane. The dibenzylidene derivative had $\lambda_{max.}$ 2270, 2510, 2660, and 2800 Å (ε 8000, 8000, 10,500, and 8500 respectively).

1-*Chloro*cyclo*decene*.—*cyclo*Decanone (5·1 g.) in benzene (15 ml.) was added, with stirring, to phosphorus pentachloride (21 g.). The mixture was kept at room temperature for 24 hr., then poured into 10% aqueous sodium carbonate (100 ml.). The solution was extracted with benzene, and the extract was dried (Na_2SO_4) and distilled, giving 1-chloro*cyclo*decene, b. p. 110°/12 mm., n_D^{26} 1·5010 (Found: C, 69·4; H, 9·9; Cl, 20·5. Calc. for $C_{10}H_{17}Cl$: C, 69·55; H, 9·9; Cl, 20·6%). (Blomquist *et al.*[4] give b. p. 121—124°/29 mm., n_D^{20} 1·5038.)

No appreciable reaction could be induced between the chloride and lithium metal in ether, even after refluxing for 24 hr.

1 : 2-*Dibromo*cyclo*decane*.—*cyclo*Decanone (21 g.) was reduced with lithium aluminium hydride (1·8 g.) in boiling ether (150 ml.) to *cyclo*decanol (21 g.), b. p. 129°/16 mm., n_D^{20} 1·4920. This was dehydrated at 250—280° with naphthalene-β-sulphonic acid (0·4 g.) to *cyclo*decene (15 g.), b. p. 74—76°/15 mm., n_D^{18} 1·4829, the infrared spectrum of which showed it to consist of approximately equal proportions of *cis*- and *trans*-isomers (cf. ref. 4).

Bromine (4·0 g.) in chloroform (10 ml.) was added dropwise to *cyclo*decene (3·7 ml.) in chloroform (5 ml.) at 0° under nitrogen. Appreciable evolution of hydrogen bromide was observed. Distillation gave a range of fractions (1·3 ml.), b. p. 110—128°/10^{-3} mm., n_D^{19} 1·5538—1·5540. These were recombined and, on dilution with pentane, deposited solid 1 : 2-*dibromo*cyclo*decane* which sublimed at 100°/0·6 mm. and then had m. p. 121° (with a transition at 102°) (Found: C, 40·1; H, 6·3; Br, 53·0. $C_{10}H_{18}Br_2$ requires C, 40·3; H, 6·1; Br, 53·6%). Attempted dehydrobromination of the dibromide by the method of Kohler *et al.*[10] gave non-homogeneous products.

Attempts to convert *cis-cyclo*decane-1 : 2-diol (m. p. 139°, prepared by reduction of sebacoin with W7 Raney-Nickel in ethanol) into dibromo*cyclo*decane by treatment with hydrogen bromide in acetic acid at room temperature gave 1-acetoxy-2-bromo*cyclo*decane, b. p. 96°/0·2 mm., n_D^{24} 1·5059 (Found: Br, 29·6. Calc. for $C_{12}H_{21}O_2Br$: Br, 28·9%) (Blomquist *et al.*,[4] give b. p. 112—116°/0·6 mm., n_D^{20} 1·5098), while similar treatment of *trans-cyclo*decane-1 : 2-diol (m. p. 50°) gave unchanged material. Reaction of the *cis*-diol with phosphorus tribromide in chloroform gave non-homogeneous products.

1-*Bromo*cyclo*decene*.—Sebacoin (100 g.), copper acetate (220 g.), acetic acid (600 ml.), and water (600 ml.) were heated under reflux for 2 hr. The solution was diluted with water (3 l.) and extracted with ether (3 × 600 ml.). The ether extract was washed with aqueous sodium hydrogen carbonate and filtered. The precipitate (5 g.) was 2 : 5-dihydroxy-2 : 6-3 : 5-bis-heptamethylene*cyclo*hexane-1 : 4-dione [11] which after sublimation in a high vacuum and recrystallisation from toluene had m. p. 255° (Found: C, 71·5; H, 9·9%; *M*, in camphor, 319. Calc. for $C_{20}H_{32}O_4$: C, 71·5; H, 9·55%; *M*, 336). Distillation of the ether layer gave *cyclo*decane-1 : 2-dione (80·8 g., 82%), b. p. 104—110°/12 mm., which crystallised from *n*-pentane and then had m. p. 41°, $\lambda_{max.}$ 2700, 2800, and 3950 Å (ε 27, 27, and 15, respectively) in EtOH (Prelog *et al.*[3] give m. p. 40°).

[10] Kohler, Tishler, Potter, and Thompson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.
[11] Raphael and Scott, *J.*, 1952, 4566.

The dione (53 g.) in ethanol (250 ml.) was treated with 95% hydrazine hydrate (40 g.), giving the bishydrazone, m. p. 108—110°, unchanged after repeated recrystallisation from ethanol [Prelog *et al.*[3] give m. p. 126—130° (decomp.); the discrepancy may be due to differences in rate of heating].

The bishydrazone (9·5 g.) was added in six portions during 30 min. to a vigorously stirred mixture of mercuric oxide (23 g.), powdered potassium hydroxide (1 g.), anhydrous sodium sulphate (20 g.), and dry toluene (100 ml.) heated under gentle reflux. After a further 2 hr., the mixture was cooled and filtered, and the solution was passed through a column of alumina (10 g.; Grade II [12]). Fractionation gave *cyclo*decyne (4·6 g.), b. p. 94°/26 mm., n_D^{20} 1·4910; Blomquist *et al.*[4] give b. p. 203—204°/740 mm., n_D^{20} 1·4950.

Hydrogen bromide, generated by slowly adding hydrobromic acid (48%, 7·5 ml.) to excess of sulphuric acid, was passed into *cyclo*decyne (4·0 g.) during 1·5 hr. Distillation gave slightly impure bromo*cyclo*decene (6·3 g.), b. p. 80—82°/1 mm., n_D^{20} 1·5230 (Found: C, 56·1; H, 8·1; Br, 35·8. Calc. for $C_{10}H_{17}Br$: C, 55·6; H, 7·9; Br, 37·0. Calc. for 1-bromo*cyclo*decene 97·5% + *cyclo*decyne 2·5%: C, 56·1; H, 8·0; Br, 35·8%).

cyclo*Dec*-1-*enecarboxylic Acid*.—1-Bromo*cyclo*decene (3·0 g.) was added to a stirred suspension of finely cut lithium (195 mg.) in ether (50 ml.) under nitrogen. After 5 min., the mixture became turbid and heat was evolved. After 4 hr., unchanged lithium (40 mg.) was filtered off through fine wire-gauze and the solution was added to powdered solid carbon dioxide (150 g.). Next day, 2N-hydrochloric acid (20 ml.) was added, and the ether layer was separated and extracted with aqueous sodium carbonate. The aqueous extract was acidified with concentrated hydrochloric acid, and the precipitate was extracted with ether. The ether extract was transferred to a vacuum retort; heating at 90—100°/10^{-4} mm. gave a sublimate (133 mg., 5%), m. p. 70—114° (Found: C, 72·6; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%). Crystallisation from aqueous methanol gave cis(?)-cyclo*dec*-1-*enecarboxylic acid*, m. p. 130—131°, $\lambda_{max.}$ 2230 Å (ε 8600) in EtOH, $\nu_{max.}$ 2800 (s) (C–H stretching), 2600 (s) (O–H stretching), 1660 (s) (C=O stretching), 1625 (s) (C=C stretching), 1440 (s) (>C–H bending), 1365 (m), 1260 (w), 1150 (w), 926 (s) (O–H bending), 886 (m), and 720 (m) cm.$^{-1}$ (Found: C, 72·6; H, 9·9%).

The acid (40·4 mg.) was hydrogenated in acetic acid (2 ml.) in the presence of platinic oxide. Uptake of hydrogen ceased when 4·6 ml. at 20°/760 mm. (Calc., 5·1 ml.) had been absorbed. The catalyst was removed by centrifuging, and the acetic acid was distilled off at 10 mm. The residue was distilled at 10^{-5} mm., giving an oil which solidified and after crystallisation from *n*-pentane had m. p. 53·5—55°. The mixed m. p. with an authentic sample of *cyclo*decanecarboxylic acid [5] (m. p. 52—53°) kindly supplied by Professor V. Prelog (E.T.H., Zürich) was 52·5—55°.

Attempted Alkenylation of Benzaldehyde.—Benzaldehyde (1·3 g.) in ether (10 ml.) was added dropwise to a stirred solution of lithium alkenyl (from 1-bromo*cyclo*decene, 2·6 g.) in ether (85 ml.) under nitrogen. After 1 hr. at room temperature, saturated ammonium chloride (20 ml.) was added, the ether layer was separated and dried (Na_2SO_4–K_2CO_3), and the solvent removed. The residue was distilled at 100—120°/10^{-3} mm., giving: (i) a *product* [*di*(cyclo*decenyl*)?] (0·6 g.), n_D^{23} 1·5255, $E_{1\,cm}^{1\%}$ <5 between 2100 and 4000 Å (Found: C, 86·5; H, 12·3. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%), which did not undergo hydrogenation (AcOH–PtO_2), but rapidly decolorised bromine water; (ii) a *product* (0·3 g.), b. p. 130—140°/10^{-3} mm., n_D^{23} 1·5655, $\lambda_{max.}$ 2280, 2510, and 2800 Å (ε 4400, 3900, and 6100, respectively) in EtOH, unchanged on addition of hydrochloric acid (Found: C, 83·6; H, 9·5. $C_{17}H_{24}O$ requires C, 83·6; H, 9·9%). Similar results were obtained on carrying out the metallation at −10°.

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Department of Chemistry, Imperial College of Science and Technology,
South Kensington, London, S.W.7. [*Received, July 16th*, 1957.]

[12] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

XUM

953. *Electrometric Titration of the Sodium Salts of Deoxyribonucleic Acids. Part V.* The Effect of Temperature.*

By R. A. Cox and A. R. Peacocke.

The dissociation curves in 0·05M-sodium chloride of herring-sperm sodium deoxyribonucleate have been studied at different temperatures by use of a continuous titration method. The reversible dissociation curves of sodium nucleate completely denatured by prior acid treatment varied with temperature and approximate values of the apparent heats of dissociation for the different titratable groups were deduced. The acid denaturation of sodium nucleate, as shown by the relative dispositions of the forward- and back-titration curves, depends on temperature and evidence is presented that sodium nucleate is only partly denatured by titration with acid to pH 2·6 at 0·4°. The reversible dissociation curve at 0·4° of the undenatured double-helical structure has been computed.

The titration curves of sodium deoxyribonucleate are anomalous, the forward-titration curve being irreversible and different from the reversible back-titration curve. The initial forward-titration with acid or alkali from pH 7 causes a permanent and irreversible rupture of hydrogen bonds, or "denaturation," through ionisation of the groups involved in them, whereas the subsequent back-titration from pH 2·5 or 12 causes reversible changes only in the state of ionisation of the molecule.[1] Hitherto the titrations have been carried out at 25° but curves obtained at other temperatures should be helpful in two respects: first, the displacement of the reversible back-titration curves with temperature should yield [2] the apparent heats of dissociation as a function of pH and thereby indicate the pH ranges in which the various groups dissociate; and secondly, the effect of temperature on the irreversible forward-titration curves might help to elucidate the mechanism of denaturation of the nucleate by acid. The titration behaviour of herring-sperm sodium deoxyribonucleate at 0·4°, 25°, and 35° is described and analysed here chiefly with the first aim. Its significance with respect to denaturation will be examined subsequently (a preliminary account has been given [3]).

Experimental

The sample of herring-sperm sodium deoxyribonucleate was that described in preceding Parts.[1,4] Solutions of the nucleate (0·141 mg. of phosphorus/ml., about 0·2%) in sodium chloride (0·05M) were titrated at the appropriate temperature with acid to a pH just below 3 and then back-titrated with alkali. The results at 25° have been reported.[1] The method of continuous titration in a cell with liquid junction and glass electrode was employed with the procedure and precautions already described.[1] The temperature was controlled by a water-bath maintained at 0·4° ± 0·2°, 25° ± 0·05°, or 35° ± 0·05°. Solutions of hydrochloric acid (0·1M), potassium hydrogen phthalate (0·05M), and sodium borate decahydrate (0·05M) were used to calibrate the glass electrode system and were assigned respectively the pH values [5] of $1{\cdot}08_5$, 4·01, and 9·39 at 0·4° and $1{\cdot}08_2$, $4{\cdot}02_5$, and 9·10 at 35°.

Results.—The titration behaviour at 0·4° is shown in Fig. 1, where curve I is the irreversible forward-titration curve and II the corresponding reversible back-titration curve from the end-point of I. Compared with the reversible back-titration curve at 25°, curve II was displaced to much lower pH values than expected from the low values of the heats of dissociation subsequently deduced (see p. 4727). This, and the relatively small difference between curves I

* Part IV, *J.*, 1956, 2646.

[1] Cox and Peacocke, *J.*, 1956, 2499.
[2] Wyman, *J. Biol. Chem.*, 1939, **127**, 1.
[3] Cox and Peacocke, *J. Polymer Sci.*, 1957, **23**, 765.
[4] Cox and Peacocke, *J.*, 1956, 2646.
[5] Steinhardt and Harris, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 335; 1940, **25**, 519; Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1943, p. 321; Hitchcock and Taylor, *J. Amer. Chem. Soc.*, 1938, **60**, 2710.

and II, suggested that II was not the reversible dissociation curve at 0·4° of completely denatured nucleate but that some hydrogen bonds had re-formed when the charge on the amino-groups ($pK_a' < 7$) was removed during back-titration. Confirmation of this was obtained in two ways. (i) The nucleate solution at pH 6—7 obtained by a complete titration cycle at 0·4° to and from pH 2·6 was submitted to a further titration cycle to and from pH 2·7 at 25° (Fig. 2). In this second, 25° cycle the forward- and back-titration curves differed (V,

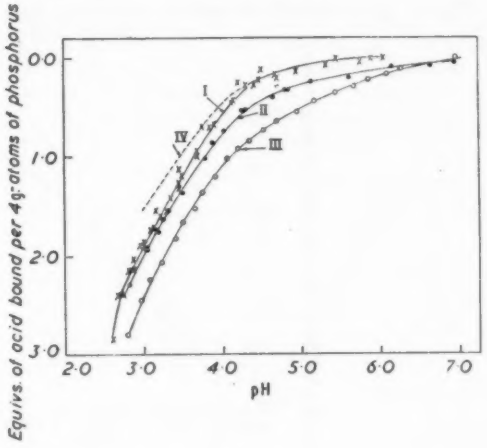
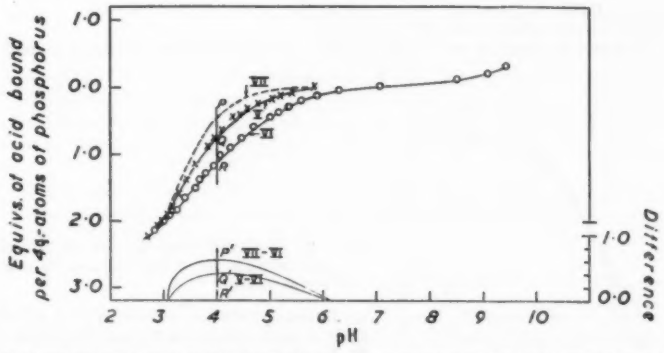


FIG. 1. *Titration curves of sodium deoxyribonucleate at* 0·4° *in* 0·05M-*sodium chloride.*

I, × Forward-titration with acid from pH 6·1. II, ● Back-titration with alkali from pH 2·6. III, ○ Titration with acid at 0·4° of a sodium nucleate sample which had previously been titrated at 25° from neutrality to pH 2·75 and back to pH 7. IV, – – – Computed reversible forward-titration curve of sodium nucleate in the double-helical configuration.

FIG. 2. *Titration curves at* 25° *in* 0·05M-*sodium chloride of sodium deoxyribonucleate previously titrated at* 0·4°.



V, × Forward-titration with acid to pH 2·75 of a nucleate sample which had been titrated at 0·4° from neutrality to pH 2·4 and back.

VI, ○ Back-titration from pH 2·75 on completion of V. VI is also the usual back-titration curve at 25° of completely denatured nucleate.

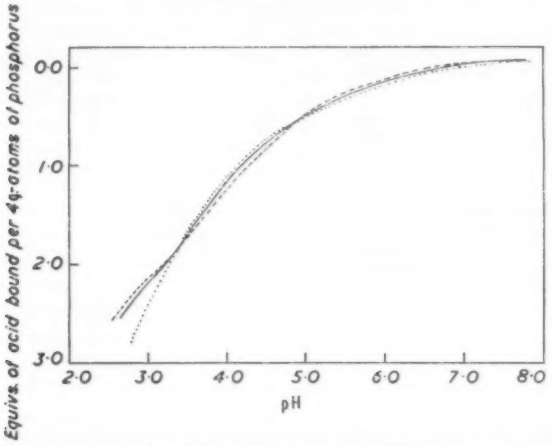
VII, – – – – Forward-titration curve with acid of nucleate not previously titrated at 0·4°.

Lower portion. Difference curves; Δ = Alkali bound along V or VII *minus* alkali bound along curve VI, ordinate scale on lower right. *P'*, *Q'*, and *R'* in the lower figure correspond to *P*, *Q* and *R*, respectively, on the titration curves.

VI, Fig. 2). From the position of V relative to VI and to VII, the forward-titration curve at 25° of a completely hydrogen-bonded nucleate, it was deduced by the method previously described [4] that this material still retained 60% of its original hydrogen bonds after having undergone the titration cycle at 0·4°. This is also illustrated by the lower comparison curves of Fig. 2 in which the ratio $Q'R'/P'R'$ was 0·6 at all pH values. (ii) The reversible dissociation curve at 0·4° of a completely denatured nucleate (III, Fig. 1) was obtained by first removing all

hydrogen bonds by a full titration cycle (to and from pH 2·75) at 25° and then repeating this at 0·4°, when forward- and back-titration both yielded the reversible curve III. The difference between II and III confirmed that II, which was also reversible, was the dissociation curve of a nucleate in which 60% of the original hydrogen bonds could re-form during back-titration from pH 2·6. Apparently at 0·4° there was an upper limit of 40% to the extent of permanent denaturation which ionisation of the amino-groups ($pK_a' < 7$) could cause.

FIG. 3. *Reversible titration curves of denatured sodium deoxyribonucleate in* 0·05M-*sodium chloride at various temperatures.*



. . . . Titration with acid at 0·4° of a solution of nucleate which has previously undergone a complete titration cycle at 25°.
——— Back-titration with alkali from pH 2·5, at 25°.
– – – – Back-titration with alkali from pH 2·6, at 35°. Each curve is the mean of several titrations.

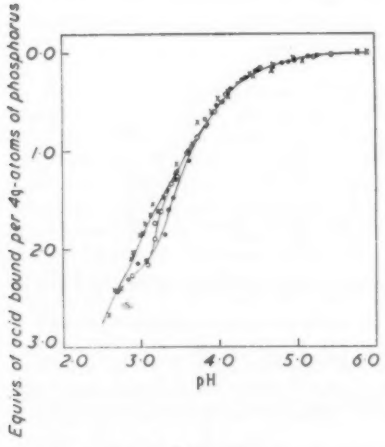


FIG. 4. *Forward-titration curves of sodium deoxyribonucleate in* 0·05M-*sodium chloride at various temperatures.*

× Forward-titration with acid from pH 6·0 at 0·4°.
○ Forward-titration with acid from pH 5·75 at 25·0°.
● Forward-titration with acid from pH 5·6 at 35·0°.

At 35° the curve obtained on back-titration from pH 2·6 was only slightly displaced from that at 25° (Fig. 3). The displacement was of the order expected from the apparent heats of dissociation deduced [6] for the similar dissociating groups in ribonucleic acids, and contrasted with that observed on lowering the temperature to 0·4°, as discussed above. At 35° the reversible back-titration curve clearly corresponded to a nucleate in the same denatured state

[6] Vandendriessche, *Compt. rend. Trav. Lab. Carlsberg*, **1951**, **27**, No. 15, 341.

as that during the back-titration at 25°, since a rise in temperature of 10° should have made denaturation by ionisation easier: the displacement at 35° was therefore the usual effect of temperature on a reversible equilibrium. The forward titration curves at 0·4°, 25°, and 35° are compared in Fig. 4. In the first stages of ionisation from pH 3·75 to 6 there was little temperature effect, so that the heats of dissociation of the hydrogen-bonded groups in this first stage, and the temperature coefficient of denaturation, must both have been small (or exactly compensatory). But after 0·8 equivalent of acid per 4 g.-atoms of phosphorus had combined, the curves for the different temperatures diverged and for a given value of the protonic charge the number of groups released from hydrogen bonds increased with temperature. This was shown by the steeper approach at 35° than at 25° of the forward- to the back-titration curve. At 25° the forward- and back-titration curves met and denaturation was complete when 2·12 equivalents of acid per 4 g.-atoms of phosphorus had combined; but at 35° this occurred when only 1·86 equivalents had combined, and this was less than the total number (1·97 per

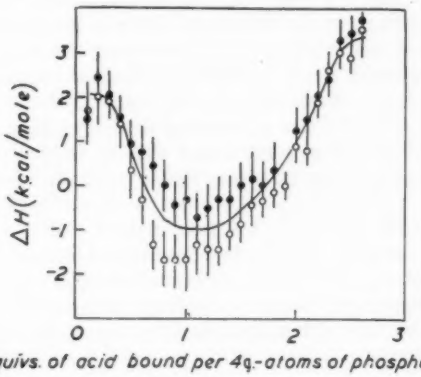


FIG. 5. *Dependence of the apparent heat of dissociation* ($\Delta H'$) *of sodium deoxyribonucleate on the acid bound* (h).

Computed from the reversible back-titration curves: ● for 0·4° and 25·0°, ○ for 0·4° and 35·0°.

Vertical lines represent uncertainty in $\Delta H'$.

4 g.-atoms of phosphorus) of hydrogen-bonded cytosine and adenine amino-groups originally present. Apparently at 35° complete ionisation of all the hydrogen-bonded groups was not necessary for complete denaturation by acid. This must have been an effect of temperature changes on denaturation by ionisation and not a direct effect on the intact hydrogen-bonded structure since, at pH 6—7, heating caused no denaturation [4] in 1 hr. unless the temperature exceeded 75°.

Heats of Dissociation.—The displacement with temperature of the curves (Fig. 3) representing the reversible dissociation of completely denatured nucleate yields [2] the apparent heats of dissociation, $\Delta H'$, of the various groups since

$$\Delta H' = -2{\cdot}303\boldsymbol{R}T^2\,[\partial(\mathrm{pH})/\partial T]_h \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $[\partial(\mathrm{pH})/\partial T]_h$ represents the rate of change of pH with temperature at a constant value of h, the number of equivalents of acid bound. Values of $\Delta H'$ were calculated from the curves in Fig. 3 for the temperature changes 0·4—25° and 0·4—35° by using the approximation [2]

$$\Delta H' = -2{\cdot}303\boldsymbol{R}T_1T_2\{(\mathrm{pH}_2 - \mathrm{pH}_1)/(T_2 - T_1)\}_h \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where subscripts 1 and 2 refer to two different temperatures ($T_2 > T_1$). The $\Delta H'$ values for the non-hydrogen-bonded nucleate are shown in Fig. 5 as a function of h. The values of $\Delta H'$ deduced from Fig. 3 for the various pH ranges, and hence for the various chemical groups, are summarised in the Table.

Discussion

It has been demonstrated that curve II (Fig. 1) obtained at 0·4°, after forward-titration at 0·4° to pH 2·6, represents the reversible dissociation curve of a nucleate in which 40% of the hydrogen bonds have been *permanently* ruptured but in which 60% can re-form during back-titration, as shown by its subsequent behaviour at 25° (Fig. 2). These observations can be interpreted in terms of the double-helical model as follows. Only

those regions of the nucleate molecule which, in spite of the ionisation of the amino-groups and disappearance of the hydrogen bonds, retain their double-helical configuration would be expected to be able to re-form complementary hydrogen bonds when the amino-groups are discharged during back-titration. In contrast, amino-groups in disordered regions which have lost the double-helical configuration would not be able to re-form the complementary hydrogen bonds on back-titration.

On this basis, curve II (Fig. 1) can be interpreted as the composite reversible dissociation curve at 0·4° of two types of region in the nucleate ions: intact double-helical regions containing 60% of the bases, and denatured, presumably disordered, regions containing 40% of the bases. This implies the existence of a *reversible* dissociation curve for a double-helical structure; along this curve the double-helical form would be approximately retained as the amino-groups ionised and complementary hydrogen bonds would re-form when the pH rose. At 25° and 35° little indication of the existence of this curve is obtained since denaturation follows quickly upon ionisation as soon as the pH is lowered. At any given pH let p, q represent the equivalents of acid bound (per 4 g.-atoms of phosphorus) along the *reversible* dissociation curves at 0·4° of the double-helical and of the completely denatured forms, respectively. Then the equivalents, r, of acid bound reversibly (per 4 g.-atoms of phosphorus) by a nucleate containing 60% of its nucleotides in double-helical regions and 40% in denatured ones is given by $r = 0{\cdot}6p + 0{\cdot}4q$. The quantities r, q are given as functions of pH by curves II and III (Fig. 1), respectively, so p can be deduced and is plotted as curve IV (Fig. 1). Presumably, if titrations could be made at sufficiently low temperatures, curve IV might be directly observed on titration with acid, no " anomaly " would be obtained, and no denaturation would be caused by ionisation. The helical structure would, as it were, be " frozen " into stability even when all the groups involved in hydrogen bonds were ionised.*

The reversible dissociations occurring along the curves III and IV can be represented as follows:

Curve III

$$\{\text{Denatured chain}\}\text{–}NH_3^+ + H_2O \rightleftharpoons \{\text{Denatured chain}\}\text{–}NH_2 \cdots (H_2O) + H^+ \quad . \quad (3)$$

Curve IV

$$\{\text{Helix}\}\text{–}NH_3^+ + X\text{–}\{\text{Helix}\} \rightleftharpoons \{\text{Helix}\}\text{–}NH_2 \cdots X\text{–}\{\text{Helix}\} + H^+ \quad . \quad (4)$$

$-NH_3^+$ and $-NH_2$ are the charged and uncharged forms of the amino-groups capable of being hydrogen-bonded (adenine and cytosine 6-amino-groups [7a] and, possibly,[7b] the guanine 2-amino-group), X is the system to which these groups are hydrogen-bonded in the double helix (the 1 : 6 –NH·CO– systems of thymine and guanine according to the *X*-ray [7a] and titration evidence,[1] and possibly the cytosine 2-oxo-group [7b]), H_2O is a solvent water molecule, the terms enclosed in braces represent the corresponding polynucleotide chains and the dotted lines are hydrogen bonds of the specific double-helical type [7] in eqn. (4) and of a non-specific type involving solvent in eqn. (3). Let the apparent acidic dissociation constants and apparent standard free energies of dissociation of the amino-groups which correspond to curves III and IV be denoted by K_{III}', K_{IV}' and by ΔG_{III}°, ΔG_{IV}°, where $\Delta G^\circ = -\boldsymbol{RT} \ln K' = 0{\cdot}4343\ \boldsymbol{RT}.\mathrm{p}K'$, with the appropriate subscripts. Then $\Delta G_{III}^\circ - \Delta G_{IV}^\circ = 0{\cdot}4343\boldsymbol{RT}(\mathrm{p}K_{III}' - \mathrm{p}K_{IV}') = 0{\cdot}4343\boldsymbol{RT}(\mathrm{pH_{III}} - \mathrm{pH_{IV}})_h$, where the last term refers to the pH displacement between curves III and IV at constant h.†

* In recent experiments at −0·4° the reversible dissociation curve of the double-helix in 0·05M-NaCl has been obtained and proved to be identical with curve IV (A. R. Peacocke and B. N. Preston, unpublished work, 1957; A. R. Peacocke, Symp. on Phosphoric Esters, Chem. Soc. Anniv. Meeting, Cambridge, 1957, Special Publication, in the press).

† Since comparison is made at constant h and only the *differences* in $\mathrm{p}K_a'$ and ΔG° between curves III and IV are employed, these equations, and what follows, apply to all the amino-groups dissociating at the particular h value.

[7] (*a*) Watson and Crick, *Nature*, 1953, **171**, 737; Peacocke, *Ricerca sci.*, 1955, **25**, 812; (*b*) Pauling and Corey, *Arch. Biochem. Biophys.*, 1956, **65**, 164.

It is clear from Fig. 1 that $K_{IV}' > K_{III}'$ but the interpretation below pH 3·75 is complicated by the presence in both III and IV of the dissociation of the 2-amino-group of guanine which, contrary to earlier ideas,[7a] may be hydrogen-bonded in the helical form.[7b] At pH values above 3·75 ($\Delta G_{III}° - \Delta G_{IV}°$) has values of +200 to +480 cal. per mole of hydrogen ions. This difference in the free energy of dissociation in the double-helical and denatured configurations can be regarded as the sum of two terms:

(i) A term which represents the differences in the non-electrostatic parts of the free energies of dissociation of the hydrogen ions in the two configurations. The most important contributor to this term would be the difference of free energy between the hydrogen bonds on the 6-amino-groups when they are linked to the 1 : 6 $-NH\cdot CO-$ systems in the double-helix and when they are linked to solvent molecules in the denatured form.

(ii) An electrostatic term representing the effects in 0·05M-sodium chloride of different electrostatic potentials at the dissociating groups in the two configurations. The magnitude of this term in 0·05M-sodium chloride can be estimated by comparing the displacements of the reversible back-titration curves (denatured form) and of the reversible portions, at low h, of the forward-titration curves (double-helical form) for a change in sodium chloride concentration from 0·05M to 0·50M, when electrostatic effects are almost completely suppressed. The two displacements differed by 0·2 pH unit which corresponds to a contribution to ($\Delta G_{III}° - \Delta G_{IV}°$) of the order of 50 cal. per mole (these figures were derived from 25° curves but should give a reasonable estimate for the relative displacements at 0·4° since the $\Delta H'$ values are all small).

The electrostatic contribution to ($\Delta G_{III}° - \Delta G_{IV}°$) is thus only of minor importance in 0·05M-sodium chloride, although at lower salt concentrations tentative calculations indicate that (i) and (ii) may be of comparable magnitude and opposite in effect. Under the conditions of this study, it therefore appears that ($\Delta G_{III}° - \Delta G_{IV}°$) is determined mainly by (i) and so by the differences in free energy of formation of the two types of hydrogen bonds in eqns. (3) and (4). The observed value of +200 to +480 cal./mole for this quantity is reasonable since the free energy of formation of a hydrogen bond is of the order of only a few thousand calories. The positive sign indicates that the specific hydrogen bonds [eqn. (4)] in the double-helical form are, not surprisingly, more stable than those involving solvent molecules [eqn. (3)] in the denatured form.

It has been concluded,[1,4] and is assumed here, that the reversible back-titration curve at 25° of denatured herring-sperm deoxyribonucleate in 0·05M-sodium chloride below pH 8 can be accounted as the summation of the dissociations of primary phosphoryl groups (pK_a ~1—2), of guanine 2-amino-groups ($pK_a' = 2·75$),* of adenine 6-amino-groups ($pK_a' = 3·5$),[1] and of cytosine (and 5-methylcytosine) 6-amino-groups ($pK_a' = 5·0$).[1,8] Spreading of the dissociation ranges by polyelectrolyte effects is small and there is no need to postulate any significant quantities of secondary phosphoryl groups.[1] Since 80% of a dissociation occurs in the range pH = $pK_a' \pm 1$, then, on the basis of the pK_a' values quoted, the amino-groups of guanine and adenine should overlap at pH below 3·75 and of adenine and cytosine at pH 4·0—4·5. At pH 3·75—4·0 only the adenine amino-group should be titrated and at pH 4·5 to neutrality only the cytosine amino-group. Hence, as described by Wyman [2] for protein dissociations, $\Delta H'$ should vary with pH where groups overlap, *viz.*, below 3·75 and at 4·0—4·5, but at pH 3·75—4·0 and above 4·5, $\Delta H'$ should remain constant at the values characteristic of the 6-amino-groups of adenine and cytosine. These pH ranges are only approximate since they have been deduced from results at 25°.

* The pK_a' for the 2-amino-group of guanine has been obtained [9] by comparison of the back-titration curves of sodium deoxyribonucleate (kindly supplied by Dr. G. L. Brown of King's College, London) from *Arbacia lixula* sperm and from avian tubercle bacilli. These samples had very different guanine contents [10] (*viz.*, 17 and 36 moles of guanine/100 moles of nucleotides respectively).

[8] Hurlen, Laland, Cox, and Peacocke, *Acta Chem. Scand.*, 1956, **10**, 793.
[9] Cox, Thesis, Birmingham, 1955.
[10] Brown, M'Ewen, and Pratt, *Nature*, 1955, **176**, 161.

The $\Delta H'$ values obtained from the reversible back-titration curves (Fig. 3) and from Fig. 5 are listed in the Table. At pH 3·75—4·35 and possibly also at pH values above 5·5, $\Delta H'$ was constant within the allowed variation and this is in accord with the above predictions. The actual $\Delta H'$ values are of the same order as those deduced by Vandendriessche [6] for ribonucleic acid, namely, about +0·9—1·4 kcal./mole at pH 5·5—5·6 and +7·8—9·0 kcal./mole at pH 9·4—9·5, although his interpretation of the former as characteristic of secondary phosphoryl groups cannot be accepted for his undegraded sample, which contained only very few of these groups.

Interpretation of the variation of $\Delta H'$ *with* pH.

h range	pH range (approx.)	$\Delta H'$ (kcal./mole)	Groups assigned
>1·4	<3·75	Varying	Guanine 2-amino Adenine 6-amino
1·4—0·85	3·75—4·35	− 1·0	Adenine 6-amino
0·85—0·4	4·35—5·5	Varying	Adenine 6-amino Cytosine 6-amino
0·10—0·4	5·5—7·0	*ca.* + 2·0	Cytosine 6-amino
—	9·5—11·0	+ 6·0	Guanine and thymine 1 : 6 –NH·CO–

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954. *Esterification of the Primary Alcoholic Groups of Carbohydrates with Acetic Acid: a General Reaction.*

By R. B. DUFF.

The primary alcoholic group of various carbohydrates is selectively esterified by 50% acetic acid at 100°. The crystalline acetylglucose obtained in this way is shown to be identical with the 6-*O*-acetyl-D-glucopyranose obtained from cultures of *Bacillus megaterium* grown on glucose media.[1] Crystalline 6-*O*-acetyl-D-galactopyranose, an unstable syrupy xylopyranose acetate, and a syrupy di-*O*-acetylglucose have also been prepared.

An estimate is made of the " total esterification " (*i.e.* including di- and tri- as well as mono-acetates) obtained with various carbohydrates including laminarin, glycogen, and amylose.

A PRELIMINARY note [1] reported the isolation of 6-*O*-acetylglucose from cultures of *Bacillus megaterium* (N.C.I.B. No. 8508). In view of the activity of the primary alcoholic group of a carbohydrate [2] an attempt was made to prepare the ester by preferential acetylation *in vitro*.

Acetic acid (50%), used at 100° for about 24 hr., was more satisfactory than the conventional reagents and the excess of acid could conveniently be removed *in vacuo* at a low temperature, to give a syrup containing unchanged glucose, 6-*O*-acetylglucose, and a di-*O*-acetylglucose as the principal components. The proportions of glucose and 6-*O*-acetylglucose were determined by quantitative paper chromatography and of the diacetate by difference, since under the conditions used the last travelled as a diffuse spot. Crystalline monoacetylglucose and syrupy diacetylglucose were separated by partition of the mixture on a cellulose column, and the monoacetate was shown to be identical with the ester from *B. megaterium*. Crystalline 6-*O*-acetylgalactose was prepared similarly; its structure follows by analogy. Moreover, 6-*O*-acetyl-glucose and -galactose failed to form

[1] Duff, Webley, and Farmer, *Nature*, 1957, **179**, 103.
[2] Sugihara, *Adv. Carbohydrate Chem.*, 1953, **8**, 1.

formaldehyde on periodate oxidation, indicating participation of the primary alcoholic groups in ester formation. In this work periodate oxidation was carried out by a modification of Reeves's method [3] in which the mixture was kept at pH 7·0 throughout the estimation (see p. 4732).

A syrupy monoacetylxylose was obtained which gave 1 mol. of formaldehyde on periodate oxidation, and the infrared spectrum indicated a pyranose structure in the ester as in the parent sugar. It seems clear that in this case the acetoxyl group is secondary. The acetylxylose was appreciably less stable than the 6-*O*-acetylhexoses. The periodate consumption of all these esters was 1 mol. less than that of the parent sugar.

A small-scale procedure was devised to examine the effect of acetic acid on sugars at various concentrations and at various temperatures. Hestrin's [4] colorimetric assay for esters was used and hence the results represent " total esterification," *i.e.*, include the proportion of di- and tri-acetyl-sugar formed as well as the monoacetyl derivative. The results (Table, p. 4734) show that appreciable amounts of esters are formed even with low concentrations of acetic acid and at lower temperatures. Hexitols give about twice the " total esterification " obtained with the parent sugars. Ketohexoses form monoacetates (presumably 1-acetates) since the primary alcoholic group on $C_{(6)}$ takes part in ring formation. These observations support the view that the primary hydroxyl group is principally concerned in these esterifications.

Some polysaccharides were examined by the above technique. In laminarin, glycogen, and amylose, about one sugar residue in every four or five was acetylated. The polysaccharides, however, appeared to be degraded, as periodate oxidation of the product from laminarin indicated an increased number of end groups. The acetylated amylose had no " blue value." During isolation by conventional methods some polysaccharides and sugars are exposed to relatively concentrated acetic acid (*e.g.*, glycogen, acidic polysaccharides such as chondroitinsulphuric acid, turanose). If acetylation without degradation takes place under these conditions the periodate consumption of the polysaccharides would be expected to be less than the true value.

Experimental

Paper Chromatography.—This was carried out by the descending technique on Whatman No. 1 paper with butan-1-ol saturated with water as a solvent. Normally a cabinet thermostatically controlled at 30° was used, but R_G values [5] were determined at room temperature (15—20°). Sugars and their esters were revealed by sprays of aniline phthalate,[6] resorcinol and hydrochloric acid,[7] aniline–diphenylamine–phosphoric acid,[8] or ammoniacal silver nitrate.[9]

Colorimetric Estimation of Acetylated Sugars.—The reaction with alkaline hydroxylamine and colour development with ferric chloride were carried out essentially as described by Hestrin,[4] and the results were calculated by comparison with a standard curve obtained with the recrystallised ester (6-*O*-acetyl-glucose and -galactose) or the chromatographically purified syrup (acetylxylose). When an E.E.L. colorimeter with small (4 ml.) tubes and a green filter was used the hexose esters and acetylxylose (0·5 mg. each) in water (1 ml.) gave colour densities of 3·48 and 3·20 respectively. The determination extended to about 1 mg. in the conditions used.

Estimation of Acetic Acid.—Acetates were hydrolysed with toluene-*p*-sulphonic acid, and the acetic acid distilled and titrated with 0·1N-alkali essentially as described by Kuhn and Roth.[10]

6-O-*Acetyl*-D-*glucopyranose.*—Glucose (1000 g.) and 50% acetic acid (100 ml.) were heated overnight in a water-bath at 100°. The excess of acid was removed at 35° *in vacuo* and the

[3] Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476.
[4] Hestrin, *J. Biol. Chem.*, 1949, **180**, 249.
[5] Hirst, Hough, and Jones, *J.*, 1949, 928.
[6] Partridge, *Nature*, 1949, **164**, 443.
[7] Forsyth, *ibid.*, 1948, **161**, 239.
[8] Buchan and Savage, *Analyst*, 1952, **77**, 401.
[9] Partridge, *Nature*, 1946, **158**, 270.
[10] Kuhn and Roth, *Ber.*, 1933, **66**, 1276.

resulting syrup separated in four lots on a powdered cellulose column (5 × 85 cm.) with water-saturated butan-1-ol. Owing to overlap it was necessary to pass some of the fractions through the washed column a second time to obtain the maximum yield of monoacetate. The ester (29 g.) crystallised on removal of solvent *in vacuo* at room temperature and recrystallised on removal of solvent from a concentrated aqueous solution. The crystals and syrupy mother-liquor were separated on a porous tile.

Four small-scale experiments were set up to determine the relative proportions of products. The syrups were dried (P_2O_5) *in vacuo* at room temperature to constant weight. Quantitative paper chromatography with the Somogyi reagent [11] (12 minutes' heating) indicated that the syrups contained 52—55% of uncombined glucose and 26—30% of 6-*O*-acetylglucose. By difference the di- and tri-acetylglucose together appeared to be 15—22%. Direct determination of the higher acetylated material was difficult because of " streaking " of the paper in that region, and the amount present will be smaller than that indicated above as some reversion products were also seen on the chromatogram.

Five recrystallisations of the crude acetylglucose from 95% ethanol gave a product with m. p. 135° alone or mixed with 6-*O*-acetyl-D-glucopyranose from *B. megaterium* cultures, $[\alpha]_D^{20}$ +48° (equil.; *c* 4·0 in H_2O), R_G 0·28 (Found: C, 42·6; H, 6·35; Ac, 18·4. Calc. for $C_8H_{14}O_7$: C, 43·2; H, 6·35; Ac, 19·4%). The infrared spectrum of the ester shows variations due to differences in the proportions of the α- and β-anomer. A description of these variations will be published later. After five recrystallisations from water the ester prepared *in vitro* gave a spectrum which was virtually identical with that of the biologically prepared material.

Periodate Oxidation of 6-O-*Acetylglucose.*—(a) *Uptake.* The periodate consumption (determined by the usual methods) was 1·7 (1 day), 3·5 (3 days), 3·7 (11 days), 3·7 (18 days) mol. The ester prepared from *B. megaterium* cultures similarly consumed 2·9 (1 day), 3·5 (7 days), 3·65 (11 days), and 3·65 (18 days) mol.

(b) *Formic acid production with hot periodate solution.* Oxidation was effected by Hirst and Jones's method,[12] and the formic acid formed was titrated potentiometrically.[13] The ester, prepared as described above, gave 4·0 mol. of formic acid in good agreement with the amount obtained from the naturally occurring ester (4·1 mol.). An unsubstituted hexose gives 5 mol. of formic acid, so it appears that the ester is oxidised without much elimination of the acetyl residue under these conditions.

(c) *Formaldehyde production by Reeves's*[3] *procedure.* (1) Unmodified. Formaldehyde–dimedone compound (m. p. 188—189°) produced (moles per mole of ester) was 0·24 (natural ester), 0·24, 0·25 (ester prepared *in vitro*).

(2) With less oxidant. The material was oxidised in separate portions with 2, 3, 4, 5, and (for comparison) 6 mol. of oxidant. The ester and glucose respectively gave 0, 0, 0, 0·26, 0·27, and 0, 0, 0, 1·0, 1·0 mol.

(3) At an acid pH. The ester was oxidised in a buffer solution of the usual composition but with the pH adjusted to 5·0 instead of 7·0. Yields were 0·20 and 0·23 mol.

(4) Removal of unused periodate with lead acetate.[14] The ester (40 mg.) was oxidised as usual with the appropriate quantities of reagents. Excess of M-lead acetate (8 ml. of aqueous solution) was added and insoluble salts were removed on the centrifuge. An aliquot part (10 ml.) of the liquid was made just acid to methyl-red with 2N-acetic acid, and buffer added (10 ml. of 1 : 1 v/v 2N-sodium acetate–N-hydrochloric acid). Addition of dimedone solution gave no immediate precipitate but a small amount of amorphous, sticky material with a low m. p. (90—110°) was slowly obtained.

For comparison, glucose (36 mg.) was treated similarly: the theoretical yield was obtained (1·0 mol.; m. p. 189°).

(5) Removal of excess of periodate with lead acetate and separation of formaldehyde by distillation. The method described in (4) was followed but an aliquot part of the periodate-free solution (10 ml.) was treated with water (60 ml.), and formaldehyde was distilled from the solution generally as described by Boyd and Logan.[15] The buffer and dimedone were added to the distillate (70 ml., including 5 ml. of water added to the receiver initially) and the compound

[11] Somogyi, *J. Biol. Chem.*, 1945, **160**, 61.
[12] Hirst and Jones, *J.*, 1949, 1659.
[13] Anderson, Greenwood, and Hirst, *J.*, 1955, 225.
[14] Akiya, *J. Pharm. Soc. Japan*, 1951, **71**, 865.
[15] Boyd and Logan, *J. Biol. Chem.*, 1942, **146**, 279.

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collected as before. In three determinations 0—0·05 mol. was obtained. Glucose gave almost the theoretical yield (0·95 mol.).

Experiments (2) and (3) show that the proportion of formaldehyde given in (1) cannot be due to over-oxidation either by the large excess of periodate present in the initial stage of the oxidation (6 mol.) or by the use of an oxidation medium buffered at pH 7·0 instead of pH 5·0 (where over-oxidation should be at a minimum). In Reeves's procedure excess of periodate is destroyed with arsenite in alkaline solution (pH 8) and the reaction is slow. It seems that either acetylglucose or its oxidation product is partly deacetylated in these conditions and is then oxidised to formaldehyde by the remaining periodate. When excess of periodate is removed rapidly and at pH 7·0 with lead acetate, and the formaldehyde is separated from the mixture as in (5), glucose, containing a free primary hydroxyl group, gave a theoretical yield of formaldehyde while acetylglucose gave none.

Experiment (4) shows that reliable results are not always obtained when formaldehyde is estimated directly in an oxidation medium containing lead acetate.

Di-O-acetylglucose.—Crude diacetylglucose, accumulated from several separations, was further purified by chromatography and obtained as a syrup, apparently homogeneous on the paper chromatogram (R_G 0·58) (Found: Ac, 30·4. Calc. for $C_{10}H_{14}O_8$: Ac, 30·6%), had $[\alpha]_D^{25}$ +50·4° (*c* 1·94 in H_2O) and gave 1·39 times the optical density given by an equal weight of 6-*O*-acetylglucose in the colorimetric assay. It seems likely that this is a 4 : 6-diacetate.[16]

6-O-*Acetyl*-D-*galactopyranose.*—Galactose (100 g.) was acetylated and the products were separated as described above. The yield of ester obtained was 33% (estimated on the crude reaction mixture by the colorimetric method). 6-O-*Acetyl*-D-*galactopyranose* formed prismatic rods (from aqueous alcohol), m. p. 138°, $[\alpha]_D^{20}$ +66° (equil.; *c* 2·0 in H_2O), R_G 0·27 (Found: C, 42·9; H, 6·1; Ac, 18·9. $C_8H_{14}O_7$ requires C, 43·2; H, 6·3; Ac, 19·4%). The infrared spectrum did not clearly indicate the type of ring structure.[17]

Periodate Oxidation of Acetylgalactose.—The methods used were as described for acetylglucose. 4 Mol. of formic acid were produced by hot periodate solution. 6-*O*-Acetylgalactose and galactose gave 0·08 and 0·94 mol. respectively of formaldehyde–dimedone compound.

Acetylxylose.—Xylose (25 g.) was acetylated and the products were separated as described above. Only 17% of esterified material was obtained (estimated colorimetrically). The syrupy product had $[\alpha]_D^{20}$ +20·6° (equil.; *c* 1·94 in H_2O) (Found: Ac, 21·5. $C_7H_{12}O_6$ requires Ac, 22·4%). The material was homogeneous on the paper chromatogram, with R_G 0·47. It was appreciably less stable than the hexose acetates and was decomposed to some extent if the aqueous solution was heated, *e.g.*, when dried on a paper chromatogram with warm air.

Infrared examination of this acetate showed absorption bands at 941, 905, and 755 $cm.^{-1}$, close to those of D-xylopyranose (935, 905, and 762 $cm.^{-1}$) and other xylopyranose derivatives.[17] Periodate oxidation as for acetylglucose [(5) above] gave 0·95 mol. of formaldehyde. Oxidation with hot periodate gave 2·7 mol. of formic acid.

Esterification of Carbohydrates with 50% Acetic Acid.—The substance (10 mg.) with 50% acetic acid (0·5 ml.) was heated at 100° for 18 hr. in a sealed tube. Acetic acid was removed *in vacuo* over solid potassium hydroxide at room temperature, and water (1 ml. or 5 ml.) added. In aliquot parts (0·1 ml. or 0·5 ml.) ester was determined as hydroxamic acid. In the Table

Substance	" Esterification units "	R_G of products	Substance	" Esterification units "	R_G of products
Glucose	100	0·28, 0·6	3-*O*-Methylglucose	130	0·30
Sorbitol	215	0·11, 0·29	Fructose	103	0·32, 0·40
Mannitol	225	0·12, 0·32	Sorbose	78	0·35, 0·41
Erythritol	187	0·27, 0·55	Arabinose	55	0·41, 0·54
Glucosamine hydrochloride...	83	0·1, 0·17, 0·22	Ribose	38	0·48
Acetylglucosamine	90	0·2, 0·43	Rhamnose	62	0·63
Dihydroxyacetone	9	0·41 (Trail)	Fucose	65	0·52
Glyceraldehyde ...	6	Trail	Sucrose	207	0·30

the values (molar) are expressed on the basis that the colorimeter reading for 1 mol. of glucose was equivalent to 100 " Esterification Units." A blank determination was performed with the parent sugar and the reading (normally small) on the E.E.L. colorimeter subtracted from that

[16] Cf. Gottlieb, Caldwell, and Hixon, *J. Amer. Chem. Soc.*, 1940, **62**, 3342; Tarkow and Stamm, *J. Phys. Chem.*, 1952, **56**, 262.

[17] Barker, Bourne, Stephens, and Whiffen, *J.*, 1954, 3468; Barker and Stephens, *J.*, 1954, 4550.

given by the acetylated product. The remainder of the solution was examined on the paper chromatogram and the R_G value(s) of the product(s) measured.

Amount of Acetylation with Variation of Acetic Acid Concentration, Temperature, and Time.—Determinations were carried out as above except that the tubes were kept at 100° for 24 hr. or as indicated. A standard of the appropriate monoacetate was used. The results, expressed in the Table as monoacetate, include higher acetylated material and are actually proportional to the total amount of acetylation.

(*a*) Acid concn. (%)	10	20	30	40	50	60	70	80	90	100%
Acetylglucose formed (%)	6·6	17·8	18·3	38	41	50	64	91	127	172
Acetylgalactose formed (%) ...		6·7		13·8		26·4		61		94
Acetylxylose formed (%)		4·5		14·5		28		64		180
(*b*) Time (hr.) of heating with 50% acid at 100°				8		18		48		
Acetylglucose formed (%)				43		46		52		
(*c*) Temperature				50°		75°		100°		
Acetylglucose formed (%) (after 24 hr. with 50% acid)				18·6		38·5		46·0		

Acetylation of Polysaccharides with Acetic Acid.—(*a*) Laminarin (5 g., provided by Dr. E. T. Dewar of the Scottish Seaweed Research Institute) was treated with 50% acetic acid as usual. The filtered solution was concentrated *in vacuo* at 30°, the acetylated polysaccharide was precipitated by pouring of the syrup into alcohol (400 c.c.) and purified by three further precipitations. The "acetylglucose content" (27%, constant) determined colorimetrically with the crystalline ester as a standard, agreed with the amount of acid obtained by hydrolysis (Found: Ac, 5·3%).

(*b*) The polysaccharide (0·5 g.) was treated with glacial acetic acid. The product was a glass, insoluble in water. It was precipitated with ether from alcoholic solution and washed with dry ether containing 5% of dry acetone (Found: Ac, 16·4%).

(*c*) Laminarin and acetylated laminarin (prepared with 50% acetic acid) were oxidised with potassium periodate in the usual way.[13] The formic acid liberated (in mmoles per anhydroglucose unit) was: laminarin, 60 (30 min.), 112 (4 days), 135 (10 days), 163 (25 days); acetyllaminarin, 39 (30 min.), 113 (4 days), 240 (10 days). Iodine was liberated in the latter case after 10 days. The results correspond to the liberation of 1 mole of formic acid from about 6·15 and 4·2 anhydroglucose units for normal and acetylated laminarin respectively.

(*d*) Glycogen (from *Mytilus edulis*; Light & Co. Ltd.) had 4·4 and 9·6% of Ac after treatment with 50 and 100% acetic acid respectively.

(*e*) Amylose (from potato starch; blue value 1·19; supplied by Dr. J. S. D. Bacon of this Institute) had 6·5% of Ac after treatment with 50% acetic acid (the acetylated material had no blue value).

(*f*) Cellulose (Whatman's standard grade ashless powder) had 0·8% of Ac after treatment with 50% acetic acid.

The yields of acetylated polysaccharides were generally poor (25% or less, except for cellulose which was recovered practically unchanged in weight), supporting the view that degradation takes place.

The author thanks Dr. V. C. Farmer of this Institute for recording and interpreting the infrared spectra and to Professor E. L. Hirst, F.R.S., for his interest.

THE MACAULAY INSTITUTE FOR SOIL RESEARCH,
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955. *Olefin Co-ordination Compounds. Part VI.* Diene Complexes of Rhodium*(I).

By J. Chatt and L. M. Venanzi.

Chloro-bridged rhodium(I) complexes of the type [diene$_2$Rh$_2$Cl$_2$] containing *cyclo*octa-1 : 5-diene, di*cyclo*pentadiene, and *cyclo*octatetraene functioning as a diene are described. Those of *cyclo*octa-1 : 5-diene (C_8H_{12}) are the most stable and their reactions have been extensively studied. The stabilities of the halogeno-complexes fall in the sequence Cl > Br > I. Amines react with the halogeno-bridged complexes to give mononuclear complexes of the type [C_8H_{12},amRhX]. There are cationic and anionic complexes of the types [C_8H_{12},diamineRh]$^+$ and [$C_8H_{12}RhCl_2$]$^-$, but they are not easily obtained as pure salts. The *cyclo*pentadienyl complex [$C_8H_{12}RhC_5H_5$] and an α-acetylacetonyl-compound [C_8H_{12}Rh acac] are described, also a dinuclear diacetate [$(C_8H_{12})_2Rh_2(OAc)_2$] in which the acetate groups are symmetrically bound, and a dinuclear methanol derivative approximating to [$(C_8H_{12})_2Rh_2(MeOH)_2$], of unknown structure.

Easily isolable olefin complexes are formed more readily by *cyclo*octa-1 : 5-diene than by any other olefin. Its silver(I), copper(I), and palladium(II) complexes are precipitated immediately when the diene is shaken with aqueous silver nitrate,[1] chlorocuprous acid, and ammonium chloropalladite [2] respectively. Its platinum(II) complexes, *e.g.*, [$C_8H_{12}PtCl_2$], in keeping with the more inert character of platinous salts, are produced more slowly but are undoubtedly the most stable olefin co-ordination complexes known, in spite of there being two double bonds attached to one platinum atom.[3] This diene is therefore eminently suitable for finding the limits in the Periodic Table of the region containing metals which form olefin complexes. At present the triangle of elements Cu(I), Pd(II), Ag(I), Pt(II), and Hg(II) is known to form reasonably stable complexes. There are also iron complexes of the type [butadieneFe(CO)$_3$] but their structures are unknown.[4]

In an attempt to extend this rather limited region of stable olefin complexes we have treated ethanolic solutions and suspensions of the commoner halides of rhodium, iridium, ruthenium, and osmium with the *cyclo*octadiene but only rhodium has given stable olefin complexes by this method.

When an ethanolic solution of rhodium trichloride trihydrate is boiled under reflux with an excess of the diene an orange solid of composition $C_8H_{12}RhCl$ slowly separates; [5] this reaction is hastened, but the quality of the product is reduced, by the addition of anhydrous sodium carbonate. The complex can also be obtained by reaction of the diene with rhodium carbonyl chloride $(CO)_4Rh_2Cl_2$ (I), and, in poorer yield, by the careful reduction of the trichloride in ethanolic solution with sodium borohydride in presence of the diene at room temperature.

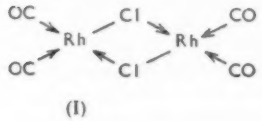
The complex, $C_8H_{12}RhCl$, is dimeric, diamagnetic, and a non-electrolyte in nitrobenzene. Its chemical properties accord with the structure (II; X = Cl) in which the rhodium atom would have a planar 4-co-ordination and be in the dsp^2 hybridised state. In this complex the rhodium is isoelectronic with palladium(II) in its 4-co-ordinated complexes, and co-ordinated exactly as in the carbonyl halide (I). Again, the close parallelism between olefin complexes and carbonyl halides is observed.

The complex (II; X = Cl) is most soluble in chlorinated solvents and moderately soluble in other organic solvents, but insoluble in water. It is converted into the corresponding bromide (X = Br) and iodide (X = I) by shaking its acetone solution with

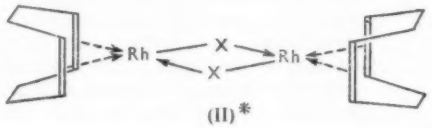
* Part V, *J.*, 1957, 3413.

[1] W. O. Jones, *J.*, 1954, 312.
[2] Chatt, Vallarino, and Venanzi, *J.*, 1957, 3413.
[3] *Idem*, *J.*, 1957, 2496.
[4] Reihlen, Gruhl, Hessling, and Pfrengle, *Annalen*, 1930, **482**, 161.
[5] Chatt and Venanzi, *Nature*, 1956, **177**, 852.

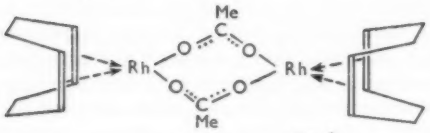
finely powdered lithium bromide and sodium iodide, respectively. The iodide is rather unstable, especially in solution. This is paralleled in the palladium(II) and platinum(II) series of olefin complexes, where the chlorides are most stable, the iodides often too unstable to be isolated, and the bromides of intermediate stability. This instability is usually attributed to increasing loosening of the olefin in the complex by increasing *trans*-effects of the halogens in the order Cl < Br < I. If this attribution is correct, its observation here indicates that the *trans*-effect operates also in complexes of rhodium(I). An attempt to obtain the diethylthio-derivative (II; X = EtS) led to decomposition, presumably owing to the high *trans*-effect of the EtS^- ion.



(I)

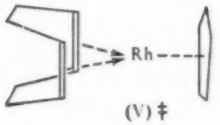


(II)*



(III)†

(IV)†



(V)‡

* The dotted lines representing the olefin-to-metal bonds imply a scheme of bonding such as that suggested in the ion $[C_2H_4PtCl_3]^-$ (see ref. 9).

† Arrows are omitted from the bonds in the bridge to emphasise the true symmetry of the bridging groups.

‡ The bond between the rhodium atom and the *cyclo*pentadienyl anion will be of the "sandwich" type.

The acetate (II; X = OAc) was prepared by boiling an acetone solution of the corresponding chloride and potassium acetate. It is quite stable. Its infrared spectrum, kindly examined for us by Dr. L. A. Duncanson, has two very strong bands at 1530 and 1419 $cm.^{-1}$, *i.e.*, in the characteristic frequency range for the carboxyl ion; otherwise the spectrum closely resembles that of the dichloro-complex (II; X = Cl). It does not give a conducting solution in nitrobenzene. These facts indicate that the acetate ion bridges symmetrically through both oxygen atoms, *e.g.*, as in (III), rather than through only one as in (IV), whose spectrum would have a band characteristic of the CO group in esters. In (III) the ring must be puckered, with intervalency angles of about 120° at the oxygen atoms to accommodate the normal intervalency angles of the acetato-groups and the rhodium atoms.

The existence of the halogen bridge in compounds (II) was confirmed by bridge-splitting reactions with amines to give mononuclear complexes:

$$[(C_8H_{12})_2Rh_2X_2] + 2\ \text{amine} \longrightarrow 2[C_8H_{12},\text{amineRhX}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

(where X = Cl, Br and I, amine = piperidine; X = Cl, amine = *p*-toluidine).

$[C_8H_{12},\text{piperidineRhI}]$ is the least stable of these derivatives and readily loses piperidine with reversion to the parent bridged iodide. This is analogous to the behaviour of amines with all classes of bridged iodide in the palladous and platinous series of complexes.[6,3] It serves to emphasise the much greater resistance to fission by nucleophilic reagents of the iodo- as compared with the chloro- and bromo-bridges between these metals, and that the

[6] Chatt and Venanzi, *J.*, 1957, 2445; 1955, 3858.

instability of the bridged iodide (II; X = I) relative to the corresponding chloride and bromide is not due to weakness at the bridge, but more probably at the olefin-to-metal bonds as required by *trans*-effect theory.

Other uncharged ligands react with the chloro-bridged complex (II; X = Cl), but of those tried (PPh_3, $AsPh_3$, Ph_2S) only the phosphine gave a product $[C_8H_{12},PPh_3RhCl_2]$ sufficiently stable to be isolated.

Similar bridge-splitting reactions with ionic halides and chelating diamines (diam) afforded evidence of the existence of unstable anionic and cationic olefin complexes:

$$[(C_8H_{12})_2Rh_2Cl_2] + 2HCl \rightleftharpoons 2H[C_8H_{12}RhCl_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$[(C_8H_{12})_2Rh_2Cl_2] + 2\ diam \rightleftharpoons 2[C_8H_{12},diamRh]Cl \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The chloro- and bromo-complexes (II; X = Cl and Br) dissolve in warm concentrated hydrochloric acid, but crystallise again when their solutions cool. They are insoluble in alkali halide solutions. In this respect the chloro-complex is exactly analogous to the bridged platinous complex $[(Et_2S)_2Pt_2Cl_4]$ and differs from $[(C_2H_4)_2Pt_2Cl_4]$ which gives the stable anion $[C_2H_4PtCl_3]^-$ with chloride solutions. This behaviour can be explained by supposing that equilibria of type (2) are established in the warm hydrochloric acid, and the halogeno-bridged complex separates before the acid on cooling.

Attempts to obtain a stable salt of $[(C_8H_{12})RhCl_2]^-$ with bulky cations, *e.g.*, $[AsPh]_4^+$, failed, but a red insoluble salt of this type with approximately the correct analysis was obtained by reaction (4).

$$[(C_8H_{12})_2Rh_2Cl_2] + dpy \longrightarrow [C_8H_{12},dpyRh][C_8H_{12}RhCl_2] \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The reaction of chelating diamines with the chloro-complex (II; X = Cl) gave salts approximating to the products of reaction (3), and by employing a bulky anion a salt of this type was obtained pure, *viz.*, $[C_8H_{12},C_2H_4(NHEt)_2Rh][BPh_4]$. 1 : 1′-Dipyridyl and *o*-phenanthroline gave beautifully crystalline red salts, presumably containing cations of this type, but repeated recrystallisation failed to give products with exactly the correct analysis. In general these compounds tended to contain too much nitrogen. Some typical examples are described in the Experimental section.

Mononuclear products were also obtained by the reaction of (II; X = Cl) with acetylacetone (acac) in alkali and with *cyclo*pentadienylsodium. The α-acetylacetonyl-compound $[C_8H_{12}Rh\ acac]$ decomposes when kept for several weeks, but the pure *cyclo*pentadienyl (V) is stable. It is exactly analogous to the carbonyl complex $(CO)_2CoC_5H_5$.[7]

Attempts to obtain rhodium complexes with other olefins and diolefins had little success. The reaction of hexa-1 : 5-diene, *cyclo*octatetraene, di*cyclo*pentadiene (tetrahydro-4 : 7-methanoindene), and styrene with $(CO)_4Rh_2Cl_2$ was not accompanied by appreciable evolution of gas, and led only to orange gummy residues. By boiling an alcoholic solution of rhodium trichloride trihydrate containing the olefin, only *cyclo*octatetraene and di*cyclo*pentadiene gave solid orange products; hexa-1 : 5-diene and dipentene both caused reduction to the metal. The *cyclo*octatetraene complex was too unstable to be purified but that of di*cyclo*pentadiene was stable and had the formula $(C_{10}H_{12})_2Rh_2Cl_2$ exactly analogous to (II; X = Cl).

Methoxides, in which one double bond of the diene has been saturated, are formed by the reaction of the diene complexes of platinous and palladous halides with anhydrous sodium carbonate in hot methanol.[2,3] By a similar reaction, $(C_8H_{12})_2Rh_2Cl_2$ (II; X = Cl) yielded a stable crystalline substance, which appeared from its analysis and molecular weight to be $(C_8H_{12})_2Rh_2(OMe)_2$, but its infrared spectrum indicates that it contains an OH group: its nature is uncertain. Its infrared spectrum is closely similar to that of the parent dichloride (II; X = Cl), suggesting that the diene has not changed during the reaction, but that methanol has added on as such. The formula $[(C_8H_{12})_2Rh_2(MeOH)_2]$ satisfactorily accounts for the spectrum, but there is no obvious structure.

It is interesting that the only olefin complexes of rhodium should contain rhodium(I),

[7] Fischer and Hafner, *Z. Naturforsch.*, 1955, **10***b*, 140.

isoelectronic with palladium(II), and that attempts to oxidise some of the rhodium(I) complexes to rhodium(II) or rhodium(III) with the theoretical quantity of chlorine led to indefinite half-oxidised products. There was no clean oxidation to the commoner tervalent state. 4-Co-ordinated rhodium(I), but not 6-co-ordinated rhodium(III), has a vacant p_z orbital which, by combination with the d_{xz} and d_{yz} orbitals, can form hybrid orbitals suitable for forming strong dative π-bonds with the anti-bonding orbitals of the diene.[8,9]

The metals known to form stable olefin complexes, all do so in a valency state which admits the possibility of *dp*-hybridisation in the dative π-bond. It may be that the *d*-orbitals alone do not give a sufficiently good overlap with the anti-bonding orbitals of the olefin to make a stable metal-to-olefin bond, and that some *p*-character is always necessary. This harmonises with the fact that olefin complexes corresponding to $Ni(CO)_4$ and such carbonyls, where there is no vacant *p*-orbital, do not appear to be obtainable. We have tried to obtain the substitution

$$C_8H_{12} + Ni(CO)_4 = C_8H_{12}Ni(CO)_2 + 2CO$$

but there was no displacement of carbon monoxide.

If a vacant *p*-orbital as well as filled *d*-orbitals is necessary for the formation of stable olefin complexes, we would expect the diene to form complexes with the iron group of metals when they are in their hitherto unknown planar 4-co-ordinated zero-valent states. Nevertheless, with decreasing valency and nuclear charge of the metal atom a point to the left of Group VIII may eventually be reached when the d_{xz}-type of orbital will reach out sufficiently to stabilise olefin complexes without the addition of *p*-character.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney, of these laboratories.

Bis(cyclo*octa*-1 : 5-*diene*)-μμ′-*dichlorodirhodium* (II; X = Cl).—*Preparation* 1. Rhodium trichloride trihydrate (1 g.) in ethanol (30 c.c.) was boiled under reflux with the diene (2 c.c.) for 3 hr. The solution was cooled, and the orange *solid* filtered off, washed with ethanol, dried, and recrystallised from acetic acid (yield 60%). It darkens from about 220°, m. p. 256° (decomp. with effervescence at 258°) (Found: C, 39·05; H, 5·0; Cl, 14·4%; *M*, ebullioscopically in 0·9% chloroform solution, 513. $C_{16}H_{24}Cl_2Rh_2$ requires C, 39·0; H, 4·9; Cl, 14·4%; *M*, 493). It is soluble in dichloromethane, moderately so in chloroform, acetic acid, and acetone, slightly soluble in ether, methanol, ethanol, and benzene, and insoluble in water. Its magnetic susceptibility, χ, is $-0{\cdot}52 \times 10^{-6} \pm 4\%$ per g.

Preparation 2. Sodium borohydride (0·5 g.) in ethanol (100 c.c.) was added during 3 hr. to a well-stirred solution of rhodium trichloride trihydrate (5 g.) and *cyclo*octa-1 : 5-diene (3 c.c.) in ethanol (125 c.c.) at 20°. The reaction is exothermic and some rhodium is deposited. After 2 days the mixture was filtered and the residue extracted with methylene chloride. The extract was taken to dryness at 15 mm., and the orange residue recrystallised from acetic acid (yield 0·67 g.). The reaction mixture still contained a considerable quantity of rhodium trichloride.

Bis(cyclo*octa*-1 : 5-*diene*)-μμ′-*dibromodirhodium* (II; X = Br).—A suspension of the dichloro-complex (II; X = Cl) (3 g.) and finely powdered lithium bromide (3 g.) in acetone (200 c.c.) was shaken until an orange opalescent solution was obtained. This was filtered and taken to dryness at 15 mm. The residue was extracted with chloroform, and the extract on evaporation at 15 mm. gave 3 g. of crude *bromo-compound*. This was purified by the action of charcoal on its cold chloroform solution and reprecipitation with light petroleum (b. p. 60—80°), then decomposing at 207—212° (Found: C, 32·8; H, 4·2. $C_{16}H_{24}Br_2Rh_2$ requires C, 33·0; H, 4·2%). Its solubility is similar to that of the chloride except that it is very soluble in chloroform and only moderately soluble in dichloromethane. It slowly decomposes in boiling solvents.

Bis(cyclo*octa*-1 : 5-*diene*)-μμ-*di-iododirhodium* (II; X = I).—A solution of the dichloro-complex (II; X = Cl) (1·3 g.) in acetone (100 c.c.) was shaken with powdered sodium iodide

[8] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332.
[9] Chatt and Duncanson, *J.*, 1953, 2939.

(0·8 g.). The brick-red *iodo-compound* (1·6 g.) formed was filtered off, washed with acetone, and dried. Recrystallised from benzene and washed with methanol it decomposed at 180—200° (Found: C, 29·2; H, 3·7. $C_{16}H_{24}I_2Rh_2$ requires C, 28·4; H, 3·6%). It decomposes in hot solvents.

Bis(cyclo*octa*-1 : 5-*diene*)-μμ′-*diacetatodirhodium* (II; X = OAc).—An acetone solution of the dichloro-complex (1 g.) and potassium acetate (1 g.) was boiled under reflux for 2 hr. The solution was then filtered and the filtrate taken to dryness at 15 mm. The residue, recrystallised from ethyl acetate, gave orange crystals of the pure *product*, m. p. 197—198° (0·54 g.) (Found: C, 44·4; H, 5·7%; *M*, ebullioscopically in 1·4% benzene solution, 597; in 1·5% solution, 587; in 0·9% solution, 554. $C_{16}H_{18}O_4Rh$ requires C, 44·5; H, 5·6%; *M*, 540). Its 10^{-3}M-solution in nitrobenzene is non-conducting.

cyclo*Octa*-1 : 5-*dienepiperidinechlororhodium*, $[C_8H_{12},C_5H_{11}N,RhCl]$.—Piperidine (0·4 c.c.) was added to the dichloro-complex (II; X = Cl) (1 g.) in dichloromethane (50 c.c.), and the yellow solution taken to dryness at 15 mm. The residue, recrystallised from light petroleum (b. p. 60—80°), gave the *product* as yellow needles, decomp. 150—170° (74%) (Found: C, 47·0; H, 7·0; N, 4·4; Cl, 11·2. $C_{13}H_{23}NClRh$ requires C, 47·0; H, 7·0; N, 4·2; Cl, 10·7%). It is a non-electrolyte in nitrobenzene. Similarly prepared were cyclo*octa*-1 : 5-*dienepiperidinebromorhodium* (71%) (from methanol), m. p. 185°, darkens 145°, sinters 165° (Found: C, 41·5; H, 6·1; N, 3·9%; *M*, ebullioscopically in 1% benzene solution, 347. $C_{13}H_{23}NBrRh$ requires C, 41·5; H, 6·2; N, 3·7%; *M*, 376), and cyclo*octa*-1 : 5-*dienepiperidineiodorhodium* (10%) [from light petroleum (b. p. 60—80°)], decomp. 150—155° (Found: C, 37·0; H, 5·4; N, 3·5. $C_{13}H_{23}NIRh$ requires C, 36·9; H, 5·5; N, 3·3%). The iodide is decomposed by boiling solvents except light petroleum, and in boiling methanol it reverts to the bridged di-iodo-complex (II; X = I).

cyclo*Octa*-1 : 5-*diene*-p-*toluidinechlororhodium*, $[C_8H_{12},p\text{-}MeC_6H_4\cdot NH_2,RhCl]$.—This *complex* separates immediately on the addition of *p*-toluidine (0·43 g.) in dichloromethane (10 c.c.) to the dichloro-complex (II; X = Cl) (1 g.) in the same solvent (50 c.c.). Recrystallised from benzene and then methanol, it forms yellow felted needles which sinter at 206°, decomp. 213—214°. It is a non-electrolyte in nitrobenzene (Found: C, 50·7; H, 6·35; N, 4·3. $C_{15}H_{21}NClRh$ requires C, 50·9; H, 6·0; N, 4·0%).

cyclo*Octa*-1 : 5-*dienetriphenylphosphinechlororhodium*, $[C_8H_{12},PPh_3RhCl]$.—Triphenylphosphine (1·07 g.) was added to a solution of the dichloro-complex (II; X = Cl) (1 g.) in dichloromethane, and the resultant solution taken to dryness at 15 mm. The residual *phosphine complex*, washed with methanol, filtered, and recrystallised from ethanol, had m. p. 146° (decomp.) (Found: C, 61·6; H, 5·6. $C_{26}H_{27}ClPRh$ requires C, 61·4; H, 5·35%).

cyclo*Octa*-1 : 5-*dienedipyridylrhodium* cyclo*octa*-1 : 5-*dienedichlororhodate* $[C_8H_{12},dpyRh][C_8H_{12}RhCl_2]$.—2 : 2′-Dipyridyl (0·4 g.) was added to the dichloro-complex (II; X = Cl) (1 g.) in dichloromethane, and the deep red solution evaporated to a small volume at 15 mm. in the cold. The red crystals were filtered off and dried. After several recrystallisations from dichloromethane–light petroleum (b. p. 40—60°) they decomposed at 215° with previous darkening at 180—190° (Found: C, 47·9; H, 5·2; N, 4·9. $C_{26}H_{32}N_2Cl_2Rh_2$ requires C, 48·1; H, 5·0; N, 4·3%). Its molecular conductivity in $1·5 \times 10^{-2}$M-nitrobenzene solution at 20° is 18 ohm^{-1} $cm.^2$.

cyclo*Octa*-1 : 5-*diene*-NN′-*diethylethylenediaminerhodium tetraphenylboron*, $[C_8H_{12},C_2H_4(NHEt)_2Rh][BPh_4]$.—The dichloro-complex (II; X = Cl) (0·6 g.) in dichloromethane was shaken with the diamine (0·6 c.c.), and sodium tetraphenylboron (1 g.) added. Sodium chloride separated and was removed. The filtrate was taken to dryness at 15 mm., and the residue taken up in a minimum of hot dichloromethane. The *product* was precipitated from this by addition of methanol (yield 0·6 g.) (Found: C, 70·5; H, 7·45; N, 4·4. $C_{38}H_{44}N_2BRh$ requires C, 70·6; H, 7·5; N, 4·3%). This salt has a molecular conductivity of 18·5 ohm^{-1} $cm.^2$ at 20° in $5·0 \times 10^{-3}$M-nitrobenzene solution.

Attempted Preparation of Dipyridyl and o-*Phenanthroline Salts containing Cations of Type* $[C_8H_{12},diamRh]^+$.—2 : 2′-Dipyridyl (0·7 g.) was added to the dichloro-complex (II; X = Cl) (1 g.) in dichloromethane (30 c.c.), and the solution evaporated at 14 mm. The residual red solid was treated with 20% perchloric acid. It changed in appearance and was filtered off, washed with water, dried, and recrystallised from methanol, the *product* forming red needles, decomp. 265—267° (effervescence) (darkens at 210—240°) (Found: C, 40·55; H, 4·3; N, 6·75. $C_{16}H_{20}O_4N_2ClRh$ requires C, 46·32; H, 4·3; N, 6·0%).

XUM

The above reaction, when conducted in ethanol, gave an orange red precipitate on addition of one equivalent of sodium tetraphenylboron (decomp. 180—188°), which was recrystallised by precipitation from dichloromethane with ethanol (Found: C, 70·4; H, 5·8; N, 4·3. $C_{42}H_{40}N_2BRh$ requires C, 73·5; H, 5·9; N, 4·1%). Further recrystallisation lowered the carbon content of the *complex*.

o-Phenanthroline (0·76 g.) in dichloromethane (20 c.c.) was added to the dichloro-complex (II; X = Cl) (1 g.) in dichloromethane (40 c.c.). The red precipitate formed at once was filtered off and recrystallised from methanol (1 g.); it decomposed at 285—290°, with darkening from 250° (Found: C, 55·7; H, 5·2; N, 7·2. $C_{20}H_{20}N_2ClRh$ requires C, 56·3; H, 4·7; N, 6·6%). Further recrystallisation of this *complex* from dilute hydrochloric acid gave a product with the following analysis: C, 56·1; H, 4·8; N, 7·7%.

When this reaction was conducted in water, and dilute nitric acid added to the solution, a red crystalline *nitrate* was obtained which recrystallised from ethanol (Found: C, 53·0; H, 4·45; N, 9·3. $C_{20}H_{20}O_3N_3Rh$ requires C, 52·5; H, 4·5; N, 9·6%).

cyclo*Octa*-1 : 5-*diene*cyclo*pentadienylrhodium*, $[C_8H_{12}RhC_5H_5]$.—The preparation was performed under nitrogen. *cyclo*Pentadienylsodium was prepared by the dissolution of sodium (0·2 g.) in *cyclo*pentadiene (10 c.c.) diluted with tetrahydrofuran (40 c.c.). This solution (10 c.c.) was then added to the dichloro-complex (II; X = Cl) (0·5 g.) in the same solvent (30 c.c.). After 12 hours' storage the solution was evaporated spontaneously in the air, leaving an orange-yellow crystalline product and a brown gum. The product was dissolved in a minimum of dichloromethane and treated with charcoal at room temperature, and the filtrate cooled to −70°. The yellow *complex* separated (m. p. 108—108·5°) (Found: C, 56·0; H, 6·1%; *M*, ebullioscopically in 0·9% acetone solution, 251. $C_{13}H_{17}Rh$ requires C, 56·5; H, 6·2%; *M*, 276). It is a non-electrolyte in nitrobenzene solution. It is very soluble in chloroform, dichloromethane, and benzene, and moderately soluble in alcohols, light petroleum, and ether. The latter solvents decompose the product with the formation of brown flocculent precipitates. The solid product is stable on long storage (>18 months).

*Bisdi*cyclo*pentadiene-μμ′-dichlorodirhodium*, $(C_{10}H_{12})_2Rh_2Cl_2$.—An ethanolic (120 c.c.) solution of rhodium trichloride trihydrate (5 g.) and di*cyclo*pentadiene (5 c.c.) was boiled under reflux for several hours, then cooled. A brown solid separated and was removed and dried. This was extracted with benzene, and the extract taken to dryness at 15 mm. to leave an orange residue (4 g.). Recrystallisation from acetic acid gave orange crystals of the *complex* which darkened at 198° and decomposed at 205—210° (Found: C, 44·4; H, 4·5. $C_{20}H_{24}Cl_2Rh_2$ requires C, 44·4; H, 4·5%).

Attempted Preparation of Methoxides.—A methanolic solution (40 c.c.) of the dichloro-bridged complex (II; X = Cl) (1 g.) was boiled under reflux for 1 hr. with anhydrous sodium carbonate (0·6 g.). The hot reaction mixture was filtered, and the yellow plates which separated as the filtrate cooled were filtered off, washed, and dried; they decomposed slowly on heating, becoming black at 180° (Found: C, 44·7; H, 6·3%; *M*, ebullioscopically in 1·1% benzene solution, 537. Calc. for $C_{18}H_{30}O_2Rh_2$: C, 44·6; H, 6·2%; *M*, 484. Calc. for $C_{18}H_{32}O_2Rh_2$: C, 44·5; H, 6·6%; *M*, 486).

Infrared Spectra.—Those of the dichloro- (II; X = Cl), diacetato- (II; X = AcO), and methoxy-complexes were kindly examined for us by Dr. L. A. Duncanson. The three spectra are very similar, indicating that the diene remains in the same form throughout. The absorption bands ($cm.^{-1}$) are listed in the table.

Infrared spectra of $[(C_8H_{12})_2Rh_2Cl_2]$, $[(C_8H_{12})_2Rh_2(OAc)_2]$, *and the "methoxide."*

$(C_8H_{12})_2Rh_2Cl_2$		$(C_8H_{12})_2Rh_2(OAc)_2$		"Methoxide"	
	993	1530 vs *	997 s	3280 s †	994
		1419 vs *			976 vw
1325 s	961 s	1327 s	960 s	1325 s	958 sh
1301 s		1299 s	953 s	1299 s	949 s
1227 m	878 w	1227 m	892 w	1225 m	889 w
1210 m		1209 m	875 s	1209 s	
1172 s	866 s	1174 m	866 s	1172 s	873 s
1153 s	831 w	1154 m	835 m	1152 s	829 w
1076 w	817 s	1075 w	817 s	1076 vs §	813 s
	795 m	1042 w	797 m		793 m
	771 s	1020 m	776 s	1004 sh	772 s

* Characteristic of $R{\cdot}CO_2^-$. † OH group. § OMe group (1030 in $CH_3{\cdot}OH$).

We are greatly indebted to Imperial Chemical Industries Limited, Billingham Division, for a gift of the *cyclo*octa-1 : 5-diene, to Dr. P. G. Owston for the measurement of the magnetic susceptibility, and to Mr. P. F. Todd for experimental assistance.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
AKERS RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS.

[*Received, June 13th,* 1957.]

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956. *The Kinetics of the Thermal Decomposition of Ammonium Perchlorate.*

By L. L. BIRCUMSHAW and T. R. PHILLIPS.

Following a previous study by Bircumshaw and Newman,[1] the decomposition of ammonium perchlorate has been investigated under varying conditions of temperature and pressure. From 400° to 440° under 20 cm. of nitrogen, the decomposition had an activation energy of 73·4 ± 1·5 kcal./mole, while at constant temperature the velocity constant of the decomposition was roughly proportional to (partial pressure of nitrogen)$^{0·6}$. We suggest that at these temperatures the decomposition is that of the vapour following evaporation of the crystals, in contrast to the decomposition of solid which takes place at lower temperatures. Some experiments on the evaporation and sublimation of the salt are described. A little tetradeuteroammonium perchlorate was prepared and its decomposition compared with that of the ordinary salt in the range 230—280°.

BIRCUMSHAW and NEWMAN [1] found that the decomposition of ammonium perchlorate *in vacuo* at 220—280° was typical of many solid decompositions in that it spread throughout the crystals from surface nuclei yielding gaseous products, and left a residue which, however, was still almost pure ammonium perchlorate. Only approximately 30% of the salt decomposed in the first instance, but the residue could be decomposed further after treatment with a solvent vapour—a process which was named "rejuvenation." The activation energy for decomposition was 18·9 kcal./mole above 240° and 29·6 below it, a change coinciding with a crystal transition from an orthorhombic to a cubic structure at 240°.

Two theories have been suggested to account for the progress of the decomposition. Bircumshaw and Newman [1] quoted a personal communication from Mr. L. A. Wiseman who suggested an electron-transfer process amongst the defects in the lattice resulting in the formation at the crystal surface of unstable perchlorate radicals; Schultz and Dekker [2] suggested that an initial step of proton transfer, $NH_4^+ + ClO_4^- \longrightarrow NH_3 + HClO_4$, is followed by a reaction at an interface where constraining forces on the ions are unbalanced. Wiseman predicted that the mechanism would change at higher temperatures, the activation energy then having a value comparable to that observed in the decomposition of other inorganic perchlorates. Experiments have been made (*a*) with tetradeuteroammonium perchlorate to compare results with Schultz and Dekker's theory and (*b*) at high temperatures with the ammonium salt where the reaction characteristics differed from those previously described.

EXPERIMENTAL

Material.—Commercial ammonium perchlorate was thrice recrystallized from distilled water, and the crystals crushed and sieved. Most experiments at high temperature were made with samples of particle size 0·089—0·052 mm. radius (*i.e.*, mesh 85—150) and usually 0·100 g. was used; the few exceptions will be indicated.

[1] Bircumshaw and Newman, *Proc. Roy. Soc.*, 1954, *A*, **227**, 115, 228.
[2] Schultz and Dekker, United States Air Force, Office of Scientific Research, Technical Note 55: 142.

Tetradeuteroammonium perchlorate was prepared by recrystallizing some of the above sample from 99·37% heavy water, the hydrogen atoms of ammonium ions being known to exchange rapidly with the solvent deuterium atoms, and the reaction having a separation factor of nearly unity.[3] Two recrystallizations gave a sample of calculated purity 99·1% which agreed well with the experimental value obtained from refractive-index measurements of the evaporated mother liquor. These crystals were crushed as before, but because of the small quantity made they were not sieved. Experiments on this material were compared with some made on ammonium perchlorate (sample " B ") which had been prepared in exactly the same manner except that distilled ordinary water was used in place of the heavy water.

Apparatus.—The experiments on the deuterated salt and those with the ammonium salt were carried out by using gas accumulatory runs in the apparatus previously described.[1] At higher temperatures this method was unsuitable and we used the apparatus illustrated in Fig. 1. It consisted of a quartz spiral spring balance enclosed in a glass chamber, the pressure within which could be measured by gauges in a conventional high vacuum line. To start an experiment, the sample was lowered into free suspension by magnetic movement of the iron bobbin *M*.

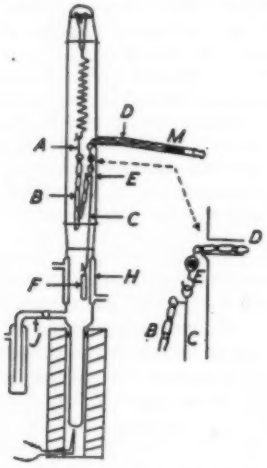


FIG. 1. *Decomposition apparatus.*

A, Pointers; *B* and *D*, glass chains; *C*, glass fibre; *F*, sample tube; *E*, weighted glass hook; *J*, vacuum line; *M*, iron bobbin.

Subsequent decomposition in the temperature-controlled oven was followed by observing the contraction of the spring.

Decomposition of Tetradeuteroammonium Perchlorate.—The salt was decomposed in an initially evacuated apparatus and the increase in pressure observed at regular intervals. Pressure–time curves were sigmoid and similar to those obtained on decomposing the ammonium salt (sample B); for both salts velocity constants for the deceleratory part of the reaction were calculated from the " contracting sphere " equation [4] $kt = \text{Const.} - [(100 - x)/100]^{\frac{1}{3}}$, where t is the time at which x% decomposition has occurred. Minimum values of k were obtained for both salts at approximately 240°, above which the ratios Z of the average velocity constant for NH_4ClO_4 to that for ND_4ClO_4 are as shown in Table 1.

TABLE 1. *Ratios of velocity constants for decomposition of* NH_4ClO_4 *and* ND_4ClO_4.

Temp.	245°	250°	255°	260°	270°
Z	0·732	0·798	0·905	0·787	0·744

These values are not those expected; Bigeleisen [5] indicated that usually a greater rate constant is observed in reactions involving " light " molecules, but exceptions to this rule are known especially for compounds containing hydrogen isotopes. Bigeleisen also states that at high temperatures the difference in activation energy between two isotopic reactions will become

[3] Bonhoeffer and Brown, *Z. phys. Chem.*, 1933, *B*, **23**, 171.
[4] Fischbeck and Spingler, *Z. anorg. Chem.*, 1939, **241**, 209.
[5] Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.

vanishingly small. This is confirmed here where the activation energies for decomposition of NH_4ClO_4 and ND_4ClO_4 are 13·60 ± 1·99 and 13·85 ± 1·52 kcal./mole respectively. The value of Z can be calculted from Schultz and Dekker's theory [2] where the expression for the velocity of penetration of the interface at which decomposition occurs is given by

$$B = (L\boldsymbol{k}TF'/\boldsymbol{h}F) \exp(-E/\boldsymbol{R}T)$$

where L is the sum of the ionic radii, F' the partition function of activated complex over all degrees of freedom except for translation along the decomposition co-ordinate, and F the partition function for the normal state of the reactants. As B can be shown to be proportional to the velocity constant, Z is the ratio of B for NH_4ClO_4 to that for ND_4ClO_4. For the cubic form of the crystals

$$F'/F = [1 - \exp(-\boldsymbol{h}\nu_2/\boldsymbol{k}T)]/[1 - \exp(-\boldsymbol{h}\nu_3/\boldsymbol{k}T)],$$

ν_2 and ν_3 being the vibration frequencies of the normal states of the positive and perchloric ions respectively along the decomposition co-ordinate. The positive-ion frequencies were calculated

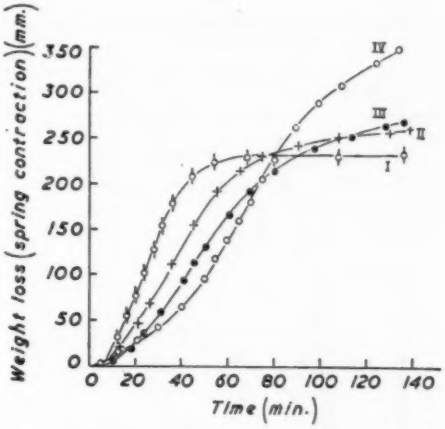


FIG. 2. *Decomposition at 280° at different nitrogen pressures.*
I, 0 cm. (accumulatory run); II, 3 cm.; III, 10 cm.; IV, 50 cm.

from the equation $\nu_2 = 0{\cdot}552(\boldsymbol{k}T/md^2)^{1/2}$ where m is the mass of the positive ion and d the dimension of the unit cell. The values obtained were substituted in the equation

$$Z = [1 - \exp(-\boldsymbol{h}\nu_2/\boldsymbol{k}T)]_{NH_4}/[1 - \exp(-\boldsymbol{h}\nu_2/\boldsymbol{k}T)]_{ND_4}$$

and at 250° the value of Z obtained was 1·28, almost the exact inverse of the experimental value.

Decomposition of Ammonium Perchlorate in the Presence of Inert Gas.—Decomposition was followed by measuring the weight loss on heating the crystals. Sublimation can be [1] prevented by small pressures of inert gas, so various pressures of nitrogen were admitted into the apparatus before the start of an experiment.

At 260—300°. In 3 cm. of nitrogen, the results were similar to those obtained in accumulatory runs.[1] A sigmoid weight loss–time curve was obtained, *e.g.*, Fig. 2(II), the initial rate, maximum rate, and the total amount of decomposition increasing with temperature. The increase in pressure due to the non-condensable evolved gases was about 2 mm. The effect of increase of inert-gas pressure at 280° is shown in Fig. 2, its main effect being the increase of the final decomposition rate with pressure. The almost complete stoppage of the reaction after 30% decomposition, as in accumulatory runs, is not observed. For comparison, the results of an accumulatory run obtained by measuring pressure increase in the evacuated apparatus are shown in Fig. 2(I). To plot them on the same axes as the weight loss experiments a separate experiment was made to establish the relation between weight loss by decomposition and pressure increase within the apparatus. A long sample tube was suspended in the furnace from a fixed suspension. Its open end projected above the furnace and collected all the sublimate, so that the weight loss on heating the sample was due to decomposition alone. The final pressure was observed and, from the known sensitivity of the spring, a pressure

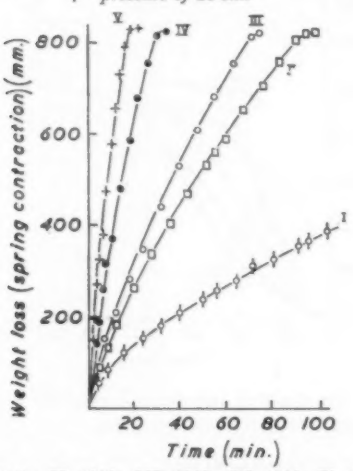
increase could then be represented by a contraction in spring length. For example, for a loss in weight of sample tube of 0·0284 g. the equivalent spring contraction, equal to weight loss multiplied by spring sensitivity, was 2·374 mm. The final pressure in the apparatus being 1·454 mm., 1 mm. (Hg) pressure increase corresponds with 2·374/1·454 ≡ 1·632 mm. spring contraction.

At 300—380°. None of the numerous experiments under various conditions gave reproducible results. Above 340°, the reaction became completely deceleratory, and at all temperatures there was no sign of its stopping before complete decomposition.

At 400—440°. The experiments were again reproducible and decomposition nearly complete, the residue never weighing more than 0·001 g. and appearing as a fragile network. Fig. 3 shows results of experiments at increasing temperatures and at a nitrogen pressure of 20 cm. At a constant temperature, 420°, but different nitrogen pressures, the results are shown in Fig. 4. Calculation showed that the velocity constants were approximately proportional to (partial pressure of N_2)$^{0\cdot6}$.

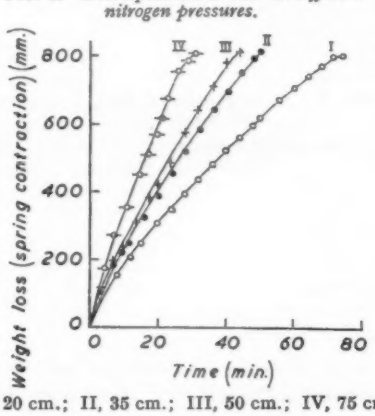
The equation $m^{2/3} = -kt + \text{const.}$ (where m is the weight of undecomposed salt at time t and k a constant) represents the decomposition curves (Fig. 5). This equation is the

FIG. 3. *Decomposition at constant nitrogen pressure of* 20 *cm.*



I, 400°; II, 410°; III, 420°; IV, 430°; V, 440°.

FIG. 4. *Decomposition at* 420° *at different nitrogen pressures.*



I, 20 cm.; II, 35 cm.; III, 50 cm.; IV, 75 cm.

integrated form of the equation for weight loss of a spherical particle when the rate of weight loss is proportional to the radius. In 20 cm. of nitrogen the following values of k were obtained:

Temp. (° c)	400	400	410	420	420	430	440	440	440
10^4k	4·82	5·17	18·8	25·3	27·8	63·3	120	106	117

Calculation by the root-mean-square method gave the equation $\log_{10} k = 20{\cdot}72 - 16{\cdot}06 \times 10^3/T$, giving an activation energy of 73·4 ± 1·5 kcal./mole.

Some experiments were also made at 420° and 240° in the apparatus described by Bircumshaw and Tayler [6] in which the salt was decomposed in a small chamber completely enclosed in a furnace, the products of the reaction accumulating in the chamber at the decomposition temperature. There was no indication of any catalysis or inhibition in these circumstances, apart from the higher reaction velocity associated with increased gas pressures.

The Evaporation and Sublimation of Ammonium Perchlorate.—In vacuo, ammonium perchlorate sublimes readily above 200°, but because of the onset of decomposition thereat the absolute vapour pressure and density could not be determined. Comparative measurements of the sublimation rates at different temperatures were made. The dissociation of ammonium chloride vapour [7] suggests that a similar mechanism may operate for the perchlorate, as

[6] Bircumshaw and Tayler, *J.*, 1956, 3405.
[7] Michaelek and Rodebush, *J. Amer. Chem. Soc.*, 1929, **51**, 746.

indicated by the fact that when calcium oxide was placed above the perchlorate in a tube in which sublimation was taking place, the amount of sublimate was considerably reduced, presumably because of adsorption of perchloric acid by the oxide.

Rate of sublimation at low pressure. Decomposition of the salt almost stops at 30% weight loss between 200° and 300°, so the loss of weight of the residue when further heated is almost entirely due to evaporation. Samples were therefore decomposed until gas evolution, as indicated by pressure measurements, ceased. The apparatus was re-evacuated and the subsequent weight loss observed. The rate of loss of weight remained fairly constant at a given temperature, the slight decrease observed towards the end of an experiment probably being due to the decrease in area of the evaporating surface. Values of the evaporation rate, r, obtained are shown in Table 3, and an activation energy for evaporation of $21{\cdot}5 \pm 2{\cdot}78$ kcal./mole was calculated from the statistically determined equation $\log_{10} r = 8{\cdot}04 - 4{\cdot}71 \times 10^3/T$.

TABLE 3.

Temp.	260°	280°	300°	306°	320°
r (mg./min.)	0·16, 0·13	0·346, 0·304	0·945, 1·11	0·712	1·04, 0·934

Sublimation in the presence of inert gas. The experiments were made in a horizontal furnace with long reaction tubes, the sublimate forming on the cool open end of the tubes which projected outside the furnace. The weight decomposed was obtained by weighing the tube before and after the experiment. The weight of sublimate was obtained by cutting off the portion of the tube on which it had formed, weighing it, dissolving the sublimate, and re-weighing. The results are shown in Table 4.

The sublimate formed at 400° was always less than that at 350°. This could result either from decomposition's being so fast at 400° that sublimation is prevented, or because the vapour of the perchlorate itself decomposes to a greater extent at 400°. The first alternative was disproved by decomposing a sample *in vacuo* at 400°; 80% sublimed, indicating that evaporation is the fastest process at this temperature.

TABLE 4.

Partial pressure of N_2 (cm.)	Temp.	Heating time (hr.)	Weight decomp. (mg.)	Weight subld. (mg.)	Partial pressure of N_2 (cm.)	Temp.	Heating time (hr.)	Weight decomp. (mg.)	Weight subld. (mg.)
3	350°	8	49·7	12·2	5	400°	8	92·3	5·0
5	350	8	52·0	10·8	10	400	8	96·0	1·7
10	350	20	65·7	2·8	15	400	8	97·6	1·3
15	350	8	85·2	0·8	0·0	400	2	20·0	80·0

The simultaneous measurement of sublimation and decomposition. Experiments were made by recording pressure increase in the initially evacuated apparatus simultaneously with the spring contraction. Using the relation (p 4744) 1·632 mm. contraction ≡ 1 mm. pressure, we drew graphs of total weight loss and weight loss by decomposition. The difference at a given time was the weight loss by sublimation. Fig. 6 shows the curves obtained at 300° where the sublimation rate for the first 30 min. of the reaction just exceeds the rate of decomposition. At a higher temperature, the difference becomes larger, while at 280°, decomposition is the faster.

The Ultraviolet Irradiation of Ammonium Perchlorate.—The experiments were confined to studying the effect of pre-irradiation before heating the sample. The sample was irradiated *in vacuo* in a quartz-windowed cell at 15° and pushed magnetically without exposure to air into a decomposition furnace at 225°. The ultraviolet source was a low-pressure mercury discharge of unknown spectral distribution. The induction period, which was arbitrarily taken as the time for the pressure of decomposition products to reach 0·03 cm., was found to be considerably reduced:

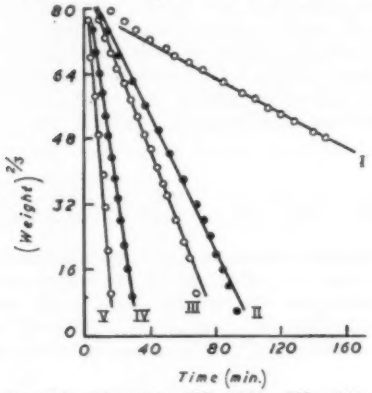
Time of irradiation (min.)	0	20	40	80	120	160	240
Average induction period (min.)	38	34	26·5	25	20	22	21·5

Garner and Maggs [8] suggested that a similar effect on irradiation of barium azide was due to photochemical formation of nuclei, but microscopical examination of the perchlorate crystals

[8] Garner and Maggs, *Proc. Roy. Soc.*, 1939, *A*, **173**, 299.

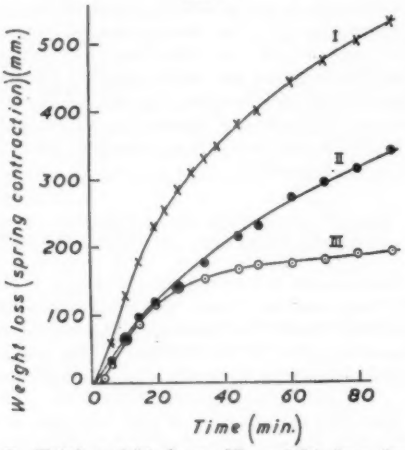
gave no evidence of this. It is generally considered that when such effects are observed the ultraviolet light increases the number of surface defects, resulting in an increased probability of nucleus formation.

FIG. 5. *Plots of* $m^{0\cdot66} = kt + \text{const.}$



I, 400°; II, 410°; III, 420°; IV, 430°; V, 440°.

FIG. 6. *Heating in evacuated apparatus at 300°.*



I, Total weight loss; II, weight loss by sublimation; III, weight loss by decomposition.

DISCUSSION

The experiments indicate that the mechanism of high-temperature decomposition is different from that operating at 200—300°. At high temperatures there is no induction period and the reaction is deceleratory throughout, the calculated activation energy is much higher, and there is no stable residue.

On heating ammonium perchlorate there are three competing reactions which can take place: (*a*) the "low" temperature reaction, (*b*) the "high" temperature reaction, and (*c*) sublimation. Process (*a*) has been shown [1] to be a true "solid" decomposition in which a decomposition interface moves through the crystal. From 380° to 440°, Table 4 shows that the predominant reaction is determined by the inert-gas pressure in the system. The sublimation experiments have shown that evaporation is the fastest reaction in this temperature range, and if there is no inert gas to impede the movement of the vapour molecules they will sublime rapidly to the cool parts of the reaction tube. In the presence of an appreciable pressure of gas, this escape is retarded, and the vapour decomposes (high-temperature reaction) with a resultant diminution of the amount of sublimate formed. Increase of gas pressure would increase this impedance, so resulting in a higher vapour concentration and explaining the enhanced decomposition rate observed.

The mechanism for decomposition is similar to that suggested for burning propellants, except that the heat transferred from the vapour decomposition to the solid is not itself sufficient to maintain the reaction. Ammonium perchlorate is only self-combustible above 68 atm.,[9] so it is considered that the back-diffusion of heat to the solid at our pressures will not be important. The burning rate of ammonium perchlorate [9] shows almost the same dependence on pressure as the decomposition rate in these experiments, *i.e.*, proportional to $p^{0\cdot5}$.

The rate-controlling process in the decomposition is probably the breakdown of the

[9] Adams, Newman, and Robins in Advisory Group of Aeronautical Research and Development (AGARD), "Selected Combustion Problems," Butterworths, London, 1954, p. 387.

perchlorate ion. Experiments on potassium perchlorate [10] at 500—550° gave an activation energy for decomposition of 69·3 kcal./mole which agrees well with that obtained for ammonium perchlorate. For the potassium salt, it is hard to envisage what reaction apart from the breakdown of the perchlorate ion could take place.

A similar vaporization process has been suggested to account for the decomposition of ammonium tri- and di-chromates, but in this case it was thought that the oxidation of ammonia was rate-controlling.[11]

The experiments on tetradeuteroammonium perchlorate do not give any additional support to Scultz and Dekker's theory, and the electron-transfer [1] theory is still preferred for decompositions at low temperatures. Proton transfer is more likely to lead to evaporation than decomposition. It is of interest that calculation of the rate of shrinkage of an evaporating sphere of perchlorate gives an answer of the same order as that for interface velocity in Schultz and Dekker's theory. Furthermore, while ultraviolet radiation affects the electronic structure of solids, it seems energetically improbable that it will cause proton transfer.

From 300° to 380° it is thought that the poor reproducibility of results is caused by the disruption of the crystal surface by evaporation, the reaction chains of the solid decomposition being broken. From the stability of the finely divided residue from the low-temperature experiments, it is clear that a certain degree of continuity is necessary for a " solid " reaction to take place. Schultz and Dekker suggested that decomposition takes place along the mosaic boundaries within the crystal, as occurs during the photolysis of silver halides.[12] From the appearance of the residue, this seems very probable, but it is not evident why the large increase in surface area which would then occur is not accompanied by an increase in evaporation rate.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15. [*Received, September 24th*, 1956. *Revised, June 26th*, 1957.]

[10] Phillips, Thesis, Birmingham, 1953.
[11] Shidlovski and Oranzherev, *Zhur. priklad. Khim.*, 1953, **26**, 25.
[12] Mitchell and Hedges, *Phil. Mag.*, 1953, **44**, 357.

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957. *Nucleophilic Substitution Reactions of Benzyl Halides. Part I. The Reaction of Benzyl Chloride with Partly Aqueous Solvents.*

By B. BENSLEY and G. KOHNSTAM.

The heat capacity of activation for the solvolysis of benzyl chloride in 50% aqueous acetone and 50% aqueous ethanol has been determined. Two mechanistic explanations can be advanced to account for all the data now available for these reactions. Hydrolysis (or ethanolysis) may involve a single bimolecular reaction path, with an appreciable contribution of the valence-bond structure involving the carbonium ion, $Ph{\cdot}CH_2^+$, to the structure of the transition state. Alternatively, a continuous " spectrum " of transition states may be available to the reactant, but only a small fraction, at most, of the total solvolysis can proceed by unimolecular mechanisms. Concurrence of only the extreme forms of the two mechanisms is not supported by the evidence.

THE solvolysis of benzyl chloride has often been studied, and it is generally accepted that the reaction with partly aqueous solvents occurs in, or near, the border-line region which marks the transition from the bimolecular (S_N2) to the unimolecular (S_N1) mechanism. No agreement exists on whether the reaction path corresponds more closely to that of a

typical S_N1 or a typical S_N2 process, and both mechanisms have been proposed.[1-5] The present paper reports the determination of the temperature coefficient of the activation energy for reaction with " 50% " acetone * and " 50% " ethanol, and discusses the conclusions which can be drawn about the reaction mechanism from the evidence now available.

Experimental

Benzyl chloride was dried ($CaCl_2$) and distilled under reduced pressure; the content of hydrolysable chloride was 99·6% of the theoretical amount; n_D^{23} was 1·5375. The methods employed in the purification of solvents and in the measurement of reaction rates were similar to those already described.[6]

Solvolysis in " 50% " Acetone and " 50% " Ethanol.—Rate measurements were carried out in duplicate or triplicate. In any one kinetic run the rate coefficient (k) was obtained from the integrated first-order rate equation as the mean of at least ten separate determinations. The results of two typical runs are given below (t in sec., k in sec.$^{-1}$):

(i) " 50% " Acetone at 80·01°; 3·765 ml. samples titrated with 0·00490N-NaOH:

$10^{-3}t$	0	2·400	4·560	6·960	9·360	12·36	14·16
Titre	0·13	1·23	2·12	3·02	3·76	4·60	5·06
10^5k	—	4·60	4·61	4·62	4·53	4·48	4·47
$10^{-3}t$	17·70	22·80	26·46	28·56	32·10	35·70	∞
Titre	5·95	6·93	7·52	7·73	8·23	8·63	10·64
10^5k	4·56	4·57	4·59	4·50	4·52	4·63	—

10^5k (mean) = 4·557; duplicate runs gave 4·581, 4·575.

(ii) " 50% " Ethanol at 80·06°, 3·765 ml. samples titrated with 0·00528N-NaOH:

$10^{-3}t$	0	0·600	1·200	1·800	2·400	3·000	4·500
Titre	0·25	1·35	2·35	3·24	4·04	4·69	6·19
10^4k	—	1·846	1·859	1·853	1·867	1·832	1·853
$10^{-3}t$	5·700	6·900	8·100	9·360	10·92	∞	
Titre	7·12	7·85	8·38	8·86	9·38	10·75	
10^4k	1·864	1·865	1·838	1·832	1·865	—	

10^4k (mean) = 1·850; a duplicate run gave 1·841.

Rate coefficients were multiplied by a small correction factor (which was determined by examining the solvolytic rate of benzotrichloride in the present solvents) in order to ensure that the results referred to the same " 50% " solvents as were employed in our earlier study of benzylidene chloride and benzotrichloride.[6] The resulting final rate coefficients are (in sec.$^{-1}$):

" 50% " Acetone	Temp.	50·01°	60·08°	69·89°	80·01°	89·90°	—
	10^4k	3·103	8·115	19·58	45·56	98·61	—
" 50% " Ethanol	Temp.	39·99°	49·99°	60·05°	69·75°	80·06°	90·02°
	10^4k	4·521	12·74	33·32	78·52	183·6	396·8

Energies and entropies of activation were calculated as previously described.[6] The observed activation energies ($E_{obs.}$) decreased with increasing temperature and did not differ by more than 0·11 kcal. mole^{-1} from the values corresponding to the " best " straight line, $E_{obs.}$ against T (see Table 1). Only a linear E–T relation can therefore be postulated since each $E_{obs.}$ was obtained from two rate coefficients (standard deviation $\leqslant$0·25%) measured at temperatures *ca.* 10° apart, and is thus subject to a standard deviation of 0·08—0·10 kcal. mole^{-1}.[7] In " 50% " acetone $dE/dT = -19 \pm 2·5$ cal. mole^{-1}, in " 50% " ethanol $dE/dT = -29 \pm 4$ cal. mole^{-1}.

* Throughout this paper a " x% " solvent refers to the mixture made up in the proportions x ml. of pure solvent to $(100 - x)$ ml. of water.

[1] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 329.
[2] Winstein, Grunwald, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700.
[3] Charlton and Hughes, *J.*, 1956, 850.
[4] Wilputte-Steinert and Fierens, *Bull. Soc. chim. belges*, 1956, **61**, 719.
[5] Simonetta and Favini, *J.*, 1954, 1840; Miller and Bernstein, *J. Amer. Chem. Soc.*, 1948, **70**, 3500.
[6] Bensley and Kohnstam, *J.*, 1956, 287.
[7] Purlee, Taft, and de Fazio, *J. Amer. Chem. Soc.*, 1955, **77**, 837.

TABLE 1. *Activation energies (E, in kcal. mole^{-1}) for the overall solvolysis of benzyl chloride.*

	Temp.	45·00°	55·00°	65·00°	75·00°	85·00°
" 50% " Acetone	$E_{obs.}$	—	20·45	20·40	20·09	19·89
	$E_{calc.}$ *	—	20·50	20·30	20·11	19·92
" 50% " Ethanol	$E_{obs.}$	20·83	20·44	20·06	19·83	19·70
	$E_{calc.}$ *	20·74	20·46	20·17	19·88	19·60

* From the " best " straight line, $E_{obs.}$ against temp.

The heat capacity of activation (ΔC^*), which represents the increase in the heat capacity of the reacting system on passage into the transition state, was obtained from the expression $\Delta C^* = dE/dT - \boldsymbol{R}$. This expression is readily derived from the conventional form of the absolute rate equation for reactions in solution.[8]

DISCUSSION

A comparison of the present results with our earlier data [6] for the S_N1 reactions of benzylidene chloride and benzotrichloride (see Table 2) shows that α-chlorination in benzyl chloride increases the rate, energy, and entropy of activation,* confirming previous observations in " 50% " acetone.[9] The negative heat capacities of activation (ΔC^*) have already been discussed in the earlier paper, where it was concluded that the loss in heat capacity on passage into the transition state arises from the increased solvation associated with the development of electric charges. This view has also been adopted to account for similar observations in the hydrolysis of *tert.*-butyl chloride [10] and esters of toluene-*p*-sulphonic acid.[11] Since both S_N1 and S_N2 solvolyses require an increase in polarity on activation, the negative ΔC^* now found in the solvolysis of benzyl chloride is to be expected and does not, by itself, provide any information about the reaction mechanism.

Mechanistic Evidence.—A considerable part of the available data suggests that the reactions of benzyl chloride with the present solvents do not occur by the unimolecular mechanism, S_N1. The rate-increase caused by *para*-methylation [12] and α-chlorination (see Table 2) results from an increase in the entropy of activation, ΔS^*, but electron-releasing substituents should accelerate S_N1 solvolysis by reducing the activation energy, E. Mechanism S_N1 for benzyl chloride is also made unlikely by the fact that here α-chlorination does not increase the solvolytic rate nearly as much as α-chlorination in benzylidene chloride (see Table 2). The accelerating effect of added hydroxide ions [9a] also argues against this mechanism, but does not exclude it completely.[13]

The present results appear to support this conclusion. Within the limits of experimental error the ratio $\Delta C^*/\Delta S^*$ is independent of the nature of the substrate for the S_N1 solvolysis of benzylidene chloride and benzotrichloride in " 50% " acetone and " 50% " ethanol (see Table 2), and in the S_N1 reactions of *para*-substituted diphenylmethyl chlorides with " 70% " and " 80% " acetone.[14] In reactions by this mechanism, and in the absence of complicating features, the degree of solvation of the transition state relatively to the

* Throughout this paper the entropy of activation refers to the quantity calculated from the observed first-order rate coefficient. This corresponds to defining the standard state of the nucleophilic reagent as its state in the solvent under consideration.

[8] Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, New York, 1941 p. 199.
[9] (*a*) Olivier and Weber, *Rec. Trav. chim.*, 1934, **53**, 867; (*b*) Hine and Lee, *J. Amer. Chem. Soc.*, 1951, **73**, 22.
[10] Tommila, Tilikainen, and Voipio, *Ann. Acad. Sci. Fennicae*, 1955, *A*, No. II.
[11] Robertson, *Canad. J. Chem.*, 1955, **33**, 1536; *J. Chem. Phys.*, 1956, **25**, 375.
[12] (*a*) Bennett and Jones, *J.*, 1935, 1815; (*b*) Olivier, *Rec. Trav. chim.*, 1930, **49**, 697.
[13] Ballinger, de la Mare, Kohnstam, and Presst, *J.*, 1955, 3641.
[14] Hughes, Ingold, and Kohnstam, unpublished results; cf. Kohnstam, Thesis, London, 1948.

initial state is by far the most important factor controlling the magnitude of ΔC^* [6,11] and ΔS^*,[6,15] and it therefore seems reasonable to assume that $\Delta C^*/\Delta S^*$ in the S_N1 reactions of organic chlorides depends only on the solvent and temperature.† On this view, the decrease in $\Delta C^*/\Delta S^*$ in passing from benzylidene chloride to benzyl chloride (see Table 2) suggests that the latter compound does not react by mechanism S_N1. This decrease can be tentatively explained in terms of some covalent attachment of a solvent molecule in the rate-determining step. Such an attachment requires a less random arrangement of this molecule than its participation in solvation, and hence a greater loss of entropy (ΔS^* is

TABLE 2. *Kinetic data for the overall solvolysis of benzyl chloride and its α-chloro-derivatives at 50°.*

(E, ΔS^*, and ΔC^* from the " best " straight line, E against T; k in sec.$^{-1}$, E in kcal., ΔS^* and ΔC^* in cal. deg.$^{-1}$.)

	" 50% " Acetone			" 50% " Ethanol		
	Ph·CH_2Cl	Ph·$CHCl_2$	Ph·CCl_3 ‡	Ph·CH_2Cl	Ph·$CHCl_2$	Ph·CCl_3 ‡
10^5k	0·3103	1·988 †	47·50 †	1·274	7·775 †	128·5 †
E	20·60	22·91	19·31	20·61	22·76	20·18
$-\Delta S^*$	22·8	11·4 †	16·2 †	19·3	9·01 †	11·5 †
$-\Delta C^*$	21 ± 2·5	29 ± 3	46 ± 4	31 ± 4	59 ± 3	73 ± 6
$\Delta C^*/\Delta S^*$	0·9	2·5 †	2·9 †	1·6	6·6 †	6·3 †

† Per replaceable chlorine atom.
‡ Data for Ph·CCl_3 extrapolated from results at lower temperatures.

generally lower in S_N2 than in S_N1 solvolysis [17]), but the loss in heat capacity is probably not greatly altered. Further work is required before mechanistic interpretations based on $\Delta C^*/\Delta S^*$ can be finally accepted. The assumption of a constant value for this ratio in S_N1 reactions is probably correct, but data for recognised S_N2 reactions are not yet available. It is also possible that ΔC^* is not a measure of the number of solvent molecules associated with the transition state in the present reactions (see p. 4752), but this would only apply if mechanism S_N1 is not operating.

On the other hand, the solvolysis of benzyl chloride in partly aqueous media also shows characteristics which are generally associated with the operation of the unimolecular mechanism. The constancy of the rate-increase on successive *ortho*-methylation has been interpreted as showing a predominantly, if not entirely, unimolecular reaction with " 50% " ethanol,[3] the introduction of *para*-substituents [12] alters the rate by factors which approach the magnitude to be expected in S_N1 solvolysis, and the retarding action of added chloride ions [18] suggests the operation of the mass-law effect which is generally considered to be specific to this mechanism;[19] it has, however, been proposed that a neutral salt effect may be responsible for this last observation.[20] Unimolecular solvolysis is usually much more sensitive to changes in the ionising power of the medium than the bimolecular process, and the data in Table 3 show that benzyl chloride behaves very much like ethyl bromide on passing from pure ethanol to " 50% " ethanol, but more like *tert.*-butyl chloride than like ethyl bromide for the other three solvent pairs. *tert.*-Butyl chloride reacts by mechanism S_N1 with all these solvents while ethyl bromide undergoes S_N2 solvolysis, except in formic acid where the reaction is largely unimolecular. The behaviour of benzyl chloride

† The S_N1 solvolysis of *tert.*-butyl chloride in " 50% " acetone also gives the required value of $\Delta C^*/\Delta S^*$.[16]

[15] (*a*) Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 25; (*b*) Buchanan and Hamann, *ibid.*, 1953, **49**, 1425; Burris and Laidler, *ibid.*, 1955, **51**, 1497.
[16] Brittain and Kohnstam, unpublished work.
[17] Gold and Jefferson, *J.*, 1953, 1409; Brown and Hudson, *ibid.*, p. 3352.
[18] (*a*) Beste and Hammett, *J. Amer. Chem. Soc.*, 1940, **62**, 2481; (*b*) Kohnstam and Rosser, unpublished results.
[19] Ref. 1, p. 365.
[20] Coburn, Grunwald, and Marshall, *J. Amer. Chem. Soc.*, 1953, **75**, 5735.

is thus consistent with an increasing tendency to react unimolecularly as the ionising power of the solvent increases,† and this conclusion derives support from the increase of $k_{50\%\ EtOH}/k_{50\%\ Me_2CO}$ for its substituted derivatives in the order p-NO_2 < p-H < p-Me.[12b]

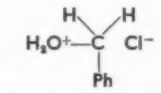
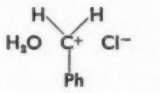
TABLE 3. *The effect of solvent changes on the rate.*

(Data from the literature for Bu^tCl,[22] for $Ph{\cdot}CH_2Cl$,[4, 15a, 23] and for EtBr [10, 2, 24].)

	Bu^tCl (25°)	$Ph{\cdot}CH_2Cl$ (50°)	EtBr (55°)
$k_{H_2O}/k_{50\%\ Me_2CO}$	125	71	6·1
$k_{H_2O}/k_{50\%\ EtOH}$	70	17	2·6
$k_{HCO_2H}/k_{50\%\ Me_2CO}$	4·6	1·6 ‡	0·04 §
$k_{50\%\ EtOH}/k_{EtOH}$	4750	26·8 †	21·9

† At 80°. ‡ At 25°. § At 100·2°.

Mechanism.—The reactions of benzyl chloride with the present solvents can be explained by assuming that the valence-bond structures (I) and (II) both make an appreciable contribution to the structure of the transition state for hydrolysis.‡ Since the rate-determining step requires covalency change by two molecules the reaction must be regarded as bimolecular (S_N2), but this is by no means inconsistent with the similarities

(I)  (II) 

between some of the reactions of benzyl chloride and S_N1 solvolysis. Most of the generally accepted characteristics of mechanism S_N2 have been established from studies on primary alkyl halides where the analogue of structure (II) is relatively unimportant. However, a bimolecular reaction in which this does not apply may approach the behaviour of a unimolecular process since the effect of changing experimental conditions on the stability of (II) is now an important factor in determining the rate.

† The values of $k_{H_2O}/k_{50\%\ EtOH}$ and $k_{H_2O}/k_{50\%\ Me_2CO}$, however, appear to indicate that this tendency is less in "50%" ethanol than in "50%" acetone, in spite of the fact that the latter solvent is the poorer ionising medium. This contradiction can be resolved if it is assumed that steric effects oppose solvation of the ionising *tert.*-butyl chloride by ethanol to a greater extent than they oppose solvation by water. $k_{H_2O}/k_{50\%\ EtOH}$ for this compound then reflects not only the effect of a better ionising medium but also the change to conditions sterically more favourable for solvation, and will therefore be larger than in compounds where this factor is less important. It has already been proposed that steric effects of this type play a greater part in the solvolysis of benzotrichloride than in the solvolysis of benzylidene chloride,[6] and the following results suggest that they are more important still when the reactant is *tert.*-butyl chloride:

Compound	$Ph{\cdot}CHCl_2$	$Ph{\cdot}CCl_3$	Bu^tCl
$k_{50\%\ EtOH}/k_{50\%\ Me_2CO}$ (25°)	3·0	2·3	1·8

Most organic halides known to undergo S_N1 solvolysis are also sterically unfavourable to bimolecular attack by nucleophilic reagents. Under these conditions steric inhibition of solvation is likely to be an important factor in determining the rate, and it is therefore necessary to treat with caution any quantitative conclusions drawn from a comparison of rates in media which differ in the nature of the solvating agent or in the proportions in which several such agents are present. This may well be at least partly responsible for the observation that the use of S_N1 rates for establishing the ionising power, Y, of a solvent [2] often leads to different values of Y when different reactants are employed, but leaves Y virtually unchanged when a reactant is replaced by a structurally similar compound.[21a]

Added, October 15th, 1957.—Other limitations of the use of Y values for the quantitative interpretation of solvolysis rates were discussed recently by Winstein *et al.*[21b]

‡ Reactions of benzyl halides with better nucleophilic reagents, and in poorer ionising solvents, have already been explained in similar terms.[25–27]

[21] (*a*) Streitwieser, *Chem. Rev.*, 1956, **56**, 618; (*b*) Winstein, Fainberg, and Grunwald, *J. Amer. Chem. Soc.*, 1957, **79**, 4146.
[22] Fainberg and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 2770.
[23] Kohnstam and Robinson, succeeding paper.
[24] Bateman and Hughes, *J.*, 1940, 940.
[25] Baker, *Trans. Faraday Soc.*, 1941, **37**, 632.
[26] de la Mare and Hughes, *J.*, 1956, 845; and references cited in ref. 3 of that paper.
[27] Swain and Langsdorf, *J. Amer. Chem. Soc.*, 1951, **73**, 2812.

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The effect of solvent changes on the rate (see Table 3) suggests that the contribution of (II) to the transition-state structure in " 50% " acetone is at least as great as that of (I), and it should therefore be considerably greater than that of (I) in " 50% " ethanol, a better ionising solvent. The latter conclusion is in qualitative agreement with the views of Charlton and Hughes.[3]

At least two concurrent processes must contribute to solvolysis in " 50% " ethanol, one for hydrolysis and the other for ethanolysis. These two processes are associated with different activation energies [23] and therefore result in a positive contribution to the observed heat capacity of activation, ΔC^*, which is calculated from the overall rate. Under these conditions ΔC^* cannot be regarded as a measure of the increase in the number of solvent molecules associated with the reactant on passage into the activated complex. This earlier interpretation also requires a constant transition-state structure, independent of temperature, and may not be justified for reaction with " 50% " acetone since there is no guarantee that the contributions of (I) and (II) are always the same. It must however be stressed that these considerations only apply once the transition state requires some covalent attachment of a solvent molecule. The earlier conclusion that the reactions do not occur unimolecularly is therefore unaffected.

The solvolytic behaviour of benzyl chloride is however also consistent with the view that hydrolysis (and ethanolysis) occurs by several reaction paths. A simple physical interpretation of ΔC^* is then impossible, but the conclusion that the whole solvolysis does not occur unimolecularly is again unaltered (see preceding paragraph). It is of interest to establish to what extent, if any, S_N1 processes contribute to the overall rate, and an upper limit for the fraction of the total solvolysis which may proceed by this mechanism (k_1/k) can be obtained from the observed value of ΔC^*. Details are given in the Appendix. All the likely errors in the assumptions made in these calculations lead to an overestimate of k_1/k, but the figures may be in error up to a factor of two in view of the accuracy with which ΔC^* is known.

The simplest case arises when S_N1 reaction, S_N2 hydrolysis, and S_N2 ethanolysis (when applicable) each occur by a single reaction path. The data for this model are given below, and it can be seen that the values of k_1/k are much too small to permit the view that only

Temp.		90°	70°	50°
$100\ k_1/k$	" 50% " Acetone	7	4·2	2·3
	" 50% " Ethanol	22	14	8

the S_N1 processes are responsible for the marked " S_N1 character " observed at 50° or less (*e.g.*, substituent and solvent effects). It therefore seems unlikely that the S_N2 processes involve the extreme form of that mechanism [*i.e.*, a very small contribution from (II)], in agreement with the general predictions by Gleave, Hughes, and Ingold about the concurrence of mechanistic extremes.[28]

Alternatively, the individual acts of molecular substitution can be considered to occur *via* any one of a continuous series of transition states which differ in the relative contributions of (I) and (II). It has already been postulated that reactions in the S_N1–S_N2 borderline region may involve a range of transition states in which both (I) and (II) are important (*i.e.*, bimolecular reaction paths only),[29] but an extension of this range to cover the mechanistic extremes has also been proposed.[30,31] If the latter view is correct, the values of k_1/k in the present reactions are certainly not greater than for the simpler model, and probably much less (for details, see Appendix).

So far there is no unambiguous evidence that S_N reactions can occur by simultaneous S_N1 and S_N2 processes. Results indicating this type of behaviour in bromine exchange

[28] Gleaves, Hughes, and Ingold, *J.*, 1935, 236.
[29] Bird, Hughes, and Ingold, *J.*, 1954, 634.
[30] Gold, *J.*, 1956, 4633.
[31] Crunden and Hudson, *J.*, 1956, 501.

with *tert.*-butyl bromide [32] are not confirmed by more recent work,[33] and the interpretation of the simultaneous hydrolysis and ammonolysis of benzoyl chloride in such terms [34] appears to require re-examination as it has been shown that at least a part of the reaction does not involve an S_N mechanism.[35] Our calculations merely give an upper limit to the fraction of S_N1 solvolysis in the present reactions *if* the two mechanisms operate concurrently: they do not prove that this concurrence exists.

It must be stressed that neither of the two mechanistic explanations now proposed for the solvolytic behaviour of benzyl chloride can explain the retarding action of added chloride ions. Passage through a single bimolecular transition state should not be subject to a mass-law effect (cf. ref. 19), and the assumption of several reaction paths leads to too small a fraction of S_N1 solvolysis to account for the observation that the presence of 0·05M-potassium chloride reduces the rate by 5% in " 50% " acetone at 70°.[18b] Further work is necessary before this difficulty can be resolved.

Appendix

Calculation of the Fraction of S_N1 Solvolysis.

If solvolysis in " 50% " acetone occurs by one unimolecular and one bimolecular reaction path (subscripts 1 and 2, respectively), the overall rate $k = k_1 + k_2$. Hence,

$$E = \boldsymbol{R}T^2(\mathrm{d} \ln k/\mathrm{d}T) = (E_1k_1 + E_2k_2)/k \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\Delta C^* = \mathrm{d}E/\mathrm{d}T - \boldsymbol{R} = (E_1 - E_2)^2k_1k_2/\boldsymbol{R}T^2k^2 + (k_1\Delta C_1^* + k_2\Delta C_2^*)/k$$

If we assume that $\Delta C_1^* = \Delta C_2^*$, this equation becomes:

$$\Delta C^* - \Delta C_1^* = (E_1 - E_2)^2k_1k_2/\boldsymbol{R}T^2k^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

ΔC_1^* was taken to be equal to ΔC^* for the ionisation of benzylidene chloride, and E_1 was obtained by assuming that α-chlorination in benzyl chloride increases the S_N1 activation energy by the same amount as α-chlorination in benzylidene chloride. By arbitrarily choosing a number of values of k_1/k at a given temperature, T_a, the corresponding values of the parameters on the right of equation (2) can be obtained at all the experimental temperatures from the overall rate at T_a, the Arrhenius equation, and equation (1). Equation (2) was considered to be satisfied when the mean of the right-hand terms over the experimental temperature range equalled $\Delta C^* - \Delta C_1^*$. k_1/k is then readily deduced.

The assumptions employed may be subject to the following errors. It is very likely that $\Delta C_1^* < \Delta C_2^*$ since the smaller dispersal of electric charges in the S_N1 transition state leads us to expect a greater degree of solvation.[36] α-Chlorination decreases ΔC^* for the ionisation of the C–Cl linkage (see Table 2), and ΔC_1^* may therefore be greater than ΔC^*(Ph·CHCl$_2$). Any steric inhibition of solvation would be greater in benzotrichloride than in benzylidene chloride; this would partially obscure the effect of α-chlorination in the S_N1 activation energy, leading to too small a value for E_1. All these errors overestimate k_1/k.

If reaction with " 50% " ethanol involves only one additional reaction path (S_N2 ethanolysis, subscript 3), k_1/k can be obtained by analogous methods. k_2/k_3 and $E_2 - E_3$ were assumed to have the values corresponding to the overall rates and activation energies for hydrolysis and ethanolysis; [23] errors resulting from these assumptions are small. In " 50% " ethanol steric inhibition of solvation is much more marked for benzotrichloride than for benzylidene chloride,[6] and we therefore assumed that α-chlorination affected the S_N1 activation energy to the same extent as in " 50% " acetone.

Alternatively, ΔC_1^* can be employed as the arbitrary parameter; k_1 is then obtained from E_1 and the constancy of the ratio $\Delta S^*/\Delta C^*$ for S_N1 reactions. This procedure reduces k_1/k by a factor of two for " 50% " ethanol, and also gives a slight reduction for " 50% " acetone.

Calculations for a continuous range of transition states were only carried out for solvolysis

[32] Le Roux and Swart, *J.*, 1955, 1475.
[33] de la Mare, *J.*, 1955, 3180.
[34] Gold, Hilton, and Jefferson, *J.*, 1954, 2756.
[35] Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154; Bunton and Lewis, *ibid.*, 1956, 180.
[36] Ref. 1, p. 346.

in " 50% " acetone. If we describe the various reaction paths by their activation energy, $E' = \Delta H^* + RT$,

$$k = (1/Nh)\int_{E'_m}^{\infty} \exp(-\Delta G^*/RT) \, . \, dE' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where E'_m is the smallest value of E', and the other symbols have their usual meaning. This equation was derived by analogy with Tolman's treatment of unimolecular gas reactions [37] and reduces to the conventional form of the absolute rate equation when ΔS^* is independent of E'.

If the relation between ΔG^* and E' is known, E'_m can be obtained from the expression for the observed activation energy, E. k_1/k can then be found by assuming that mechanism S_N1 operates when $E' \geqslant E_1$, where E_1 has the same value as in the simpler model already discussed. Unfortunately ΔG^* is not a known function of E'. We therefore employed a number of arbitrary, but *a priori* reasonable, functions which involved an unknown parameter, and accepted those values of this parameter which satisfied the analogue of equation (2) with $\Delta C_1^* = \Delta C^*(\mathrm{Ph{\cdot}CHCl_2})$, as before.

The use of a number of different functions for ΔG^* gave smaller k_1/k values than the simpler model. The values are probably too large for the reasons already discussed, and also because we always chose ΔG^* as a single-value function of E'. It is quite likely that E' passes through a minimum with changing transition-state structure, and contributions from some bimolecular processes to the rate may therefore have been neglected. Errors in k_1/k from the assumptions involved in setting up equation (3) are probably not unduly large.

We are greatly indebted to Professor C. K. Ingold, Professor E. D. Hughes, and Mr. G. R. Martin for valuable comments, and to the Council of the Durham Colleges for the award of a Postgraduate studentship (to B. B.).

THE UNIVERSITY SCIENCE LABORATORIES,
SOUTH ROAD, DURHAM. [*Received, May 23rd,* 1957.]

[37] Fowler and Guggenheim, " Statistical Thermodynamics," Cambridge Univ., London, 1939, p 521.

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958. *The Preparation and Properties of Acetochloroglucosamine and its Use in the Synthesis of* 2-*Acetamido*-2-*deoxy*-β-D-*glucosides* (N-*Acetyl*-β-D-*glucosaminides*).

By D. H. LEABACK and P. G. WALKER.

A new preparation of acetochloroglucosamine is described. This compound has been used in the synthesis of alkyl and aryl 2-acetamido-2-deoxy-β-D-glucosides. In wet solvents it is transformed into 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucose hydrochloride, properties and reactions of which are described.

METHODS were required for the synthesis of alkyl and aryl 2-acetamido-2-deoxy-β-D-glucosides (*N*-acetyl-β-D-glucosaminides) for use as substrates in a study of the enzyme " *N*-acetyl-β-glucosaminidase." [1] Such alkyl derivatives have been prepared by the condensation [2] of alcohols with 2-acetamido-2-deoxy-D-glucose, and the phenyl compound by condensation of phenol with 2-amino-2-deoxyglucose (glucosamine) penta-acetate.[3] Both these reactions gave mixtures of α- and β-glycosides from which the β-isomers were separated by column chromatography [2] or fractional crystallisation.[4]

Moggridge and Neuberger [5] claimed to have prepared acetobromoglucosamine, but

[1] Borooah, Leaback, and Walker, *Biochem. J.*, 1957, **65**, 15P.
[2] Zilliken, Rose, Braun, and Gyorgy, *Arch. Biochem. Biophys.*, 1951, **54**, 392.
[3] Helferich and Iloff, *Z. physiol Chem.*, 1933, **221**, 252.
[4] Roseman and Dorfman, *J. Biol. Chem.*, 1951, **191**, 607.
[5] Moggridge and Neuberger, *J.*, 1938, 745.

were unable to use their product in the synthesis of 2-acetamido-2-deoxy-β-D-glucosides. Kuhn and Kirschenlohr,[6] however, described the preparation, in good yield, of such alkyl glycosides by condensation of alcohols with acetobromoglucosamine which was said to have been prepared by Moggridge and Neuberger's method. In our hands, Kuhn and Kirschenlohr's method was successful provided that acetobromoglucosamine was used as an uncrystallised syrup. Attempts to crystallise acetobromoglucosamine from the syrup invariably resulted in the isolation of 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucose hydrobromide, thus confirming the work of Micheel, Van de Kamp, and Wulff.[7] Unsuccessful attempts were made to employ acetobromoglucosamine in the synthesis of aryl 2-acetamido-2-deoxy-β-D-glucosides.[8] Other reports of difficulty in the use of acetobromoglucosamine have appeared.[7,9,10]

Baker *et al.*[9] described the preparation of crystalline acetochloroglucosamine (2-acetamido-3 : 4 : 6-tri-*O*-acetyl-1-chloro-2-deoxy-α-D-glucose) (II), which was employed successfully in the synthesis of an *N*-glycosylpurine and of 2-acetamido-2-deoxy-α-D-glucose 1-phosphate.[10] The present paper describes further work on the preparation and properties of acetochloroglucosamine and its use in the synthesis of alkyl and aryl 2-acetamido-2-deoxy-β-D-glucosides.[11]

Much of the present work was carried out with acetochloroglucosamine prepared according to the method of Baker *et al.*, by the action of ether, acetic anhydride, and hydrogen chloride on the β-penta-acetate (I). Difficulties were experienced with this preparation: frequently the penta-acetate did not dissolve in the reagent or was precipitated therefrom. This was even more marked in the preparation of acetochloroglucosamine from the α-penta-acetate (VII), and has been attributed to the basicity of the *N*-acetyl group.[12] The difficulties have been overcome by using dry hydrogen chloride and acetic anhydride as the reagent: reaction is faster with the β- than with the α-penta-acetate.

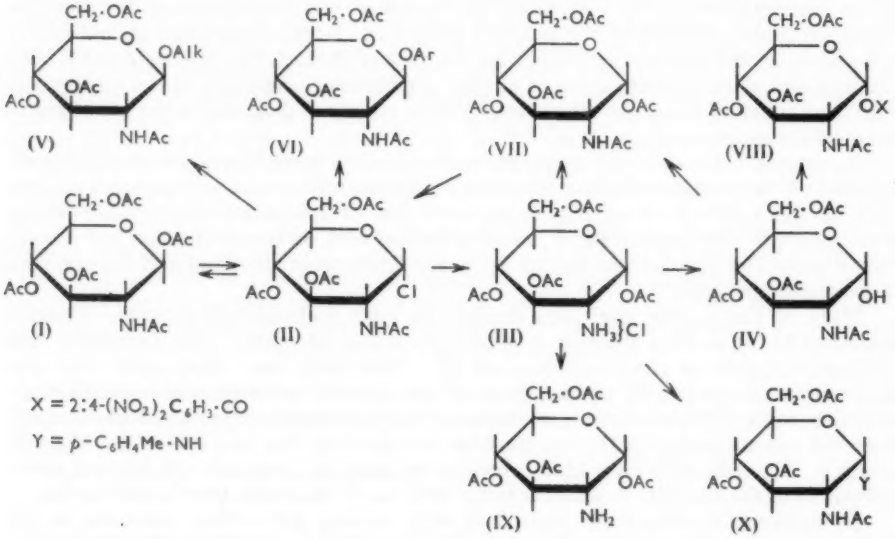
Acetochloroglucosamine and methyl or ethyl alcohol, with silver carbonate as the condensing agent, gave good yields of methyl and ethyl 2-acetamido-3 : 4 : 6-tri-*O*-acetyl-2-deoxy-β-D-glucoside (V). Removal of the *O*-acetyl groups from the ethyl compound with ammoniacal methanol brought about some anomerisation.[13] While the present work was in progress, Morel[14] reported briefly that the alkyl β-D-glycosides can be prepared from acetochloroglucosamine with mercuric cyanide as the condensing agent.

Aryl tetra-acetyl-2-amino-2-deoxy-β-D-glucosides (VI) were prepared by condensing acetochloroglucosamine with the appropriate phenol under conditions similar to those used by Glaser and Wulwek;[15] no single method was found convenient for removal of *O*-acetyl groups from all the tetra-acetates prepared (Table 2). Glaser and Wulwek reported that *o*-nitrophenyl tetra-*O*-acetyl-β-D-glucoside gave an anomalous positive optical rotation; the 2-amino-compound is similar in this respect. In conditions known to give aryl α-glycosides with acetobromo-sugars,[16] acetochloroglucosamine gave phenyl tetra-acetyl-2-amino-2-deoxy-β-D-glucoside.

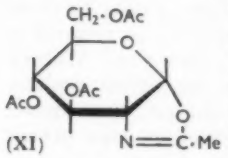
Acetochloroglucosamine (II) is stable in dry solvents but in the presence of water is converted into 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucose hydrochloride (III). Inouye, Kitaoka, and Ochiai[17] independently came to a similar conclusion. The infrared spectra of compounds (II) and (III) agree with the proposed structures (Table 1); further, compound (III) was converted into the free base (IX) which had constants similar to those

[6] Kuhn and Kirschenlohr, *Chem. Ber.*, 1953, **86**, 1331.
[7] Micheel, Van de Kamp, and Wulff, *Chem. Ber.*, 1955, **88**, 2011.
[8] Leaback and Walker, unpublished results.
[9] Baker, Joseph, Schaub, and Williams, *J. Org. Chem.*, 1954, **19**, 1786.
[10] Leloir and Cardini, *Biochim. Biophys. Acta*, 1956, **20**, 33.
[11] Cf. Leaback and Walker, *Chem. and Ind.*, 1956, 1017.
[12] Baker, Joseph, and Schaub, *J. Amer. Chem. Soc.*, 1955, **77**, 5905.
[13] Cf. Hough and Taha, *J.*, 1956, 2042.
[14] Morel, *Experentia*, 1956, **12**, 419.
[15] Glaser and Wulwek, *Biochem. Z.*, 1924, **145**, 514.
[16] Helferich and Jung, *Annalen*, 1954, **589**, 77.
[17] Inouye, Kitaoka, and Ochiai, *Bull. Agric. Chem. Soc. Japan*, 1956, **20**, 157.

reported by Micheel *et al.*[7] for this compound. The transformation (II) ⟶ (III) is particularly rapid in nitromethane and acetonitrile, and is accelerated by free acid. A similar reaction probably occurred in our unsuccessful attempts to crystallise acetobromoglucosamine.



Compound (III) had physical properties similar to those of the corresponding hydrobromide described by Micheel *et al.*,[7] and to those of the β-anomer;[18] however, it differs from the latter in that, in aqueous solution, its optical rotation falls slowly. The process is faster in presence of pyridine or sodium acetate and is similar to that described by Micheel *et al.*[7] for the corresponding hydrobromide. Micheel *et al.* ascribed this fall in rotation to the conversion of 1 : 3 : 5 : 6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucose hydrobromide into the oxazoline (XI). White[19] started with what was probably 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucose hydrobromide (then thought to be acetobromoglucosamine) and claimed to have prepared this oxazoline (XI). By White's method, Micheel *et al.*[7] converted the 1 : 3 : 4 : 6-tetra-acetate hydrobromide into what was said to be the oxazoline (XI); under anhydrous conditions the product was then converted into 2-amino-2-deoxy-α-D-glucose penta-acetate and the 1-(3 : 5-dinitrobenzoate) 3 : 4 : 6 : *N*-tetra-acetate (VIII).



Starting from the hydrochloride (III) and using conditions similar to White's, we have isolated a product with constants similar to those reported for the oxazoline; however, we consider this product to be the tetra-acetate (IV) since (i) it has an infrared band at 3300 cm.$^{-1}$ corresponding to the groups –NH– and/or –OH (see Table 1), (ii) it was converted under anhydrous conditions into compounds (VII) and (VIII), and (iii) its optical rotation (in water) fell (mutarotation?) to a value identical with the equilibrium value obtained when the salt (III) was treated at room temperature with a solution of sodium acetate.

[18] Bergman and Zervas, *Ber.*, 1931, **64**, 978.
[19] White, *J.*, 1940, 428.

TABLE 1. *Infrared spectra (max. in cm.$^{-1}$).*

Compound	–OH and –NH– Region	$NH_3^+ X^-$	*O*-Acyl	Amide I & II	2*a* Band
(II)	3250	None	1735	1640, 1540	755
(III)	None	3000—2500	1750	None	None
Hydrobromide analogous to (III)	None	3000—2500	1750	None	None
(IV)	3300	None	1735	1650, 1540	None

TABLE 2. *Removal of O-acetyl groups from aryl 2-acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucosides.*

Aryl	Products [a] Yield (%)	M. p. (decomp.)	$[\alpha]_D$ [c]	Formula	Found (%) C	H	N	Required (%) C	H	N
Ph	71 [b]	249°	− 8·4	$C_{14}H_{19}O_6N$	56·3	6·6	4·9	56·6	6·4	4·7
p-C_6H_4Ac	55 [c]	224—225	− 5·5	$C_{16}H_{21}O_7N$	58·8	6·2	4·5	59·6	6·2	4·4
o-NO_2-C_6H_4	69 [d]	192—194	−33·1	$C_{14}H_{18}O_8N_2$	49·2	5·3	8·2	49·1	5·3	8·2
p-NO_2-C_6H_4	83 [d]	204	−18·6	$C_{14}H_{18}O_8N_2$	48·8	5·4	8·2	49·1	5·3	8·2
1-$C_{10}H_7$	92 [d]	244—246	−64·5	$C_{18}H_{21}O_6N$	60·9	5·8	4·0	62·2	6·0	4·0

[a] Recryst. from H_2O. [b] Prep. by $Ba(OMe)_2$–MeOH (Isbell, *Bur. Stand. J. Res.*, 1930, **5**, 1185). [c] As (*b*) but in 1 : 1 MeOH–$CHCl_3$. [d] Prep. by Westphal and Schmidt's method (*Annalen*, 1952, **575**, 84). [e] In H_2O (0·2—0·5% solution) at *ca.* 20°.

Bertho and Koziollek [20] prepared 2-acetamido-2 : 3 : 4 : 6-tetra-*O*-acetyl-1 : 2-dideoxy-1-*p*-toluidino-D-glucopyranose by treating *p*-toluidine with "acetobromoglucosamine" prepared by Moggridge and Neuberger's method.[5] We treated the salt (III) with *p*-toluidine under Bertho and Koziollek's conditions [20] and isolated the same compound (X). On removal of *O*-acetyl groups, the product had constants similar to those described for 2-acetamido-1 : 2-dideoxy-1-*p*-toluidino-D-glucopyranose and behaved chromatographically as did this compound prepared by the condensation of 2-acetamido-2-deoxy-D-glucose and *p*-toluidine.[20] The nature of the reaction between the salt (III) and *p*-toluidine is under investigation but it is thought that the amide (IV) may be involved.

Table 1 summarises the infrared data presented in this paper.

EXPERIMENTAL

Paper chromatography was carried out on Whatman No. 1 filter paper by the descending method with (*a*) butan-1-ol–ethanol–water (4 : 1 : 5 v/v) or (*b*) butan-1-ol–pyridine–water (6 : 4 : 3 v/v), and the separated substances were detected by Rydon and Smith's method.[21]

All the compounds except acetochloroglucosamine were dried overnight at 100° (over P_2O_5) before analysis. Infrared spectra were determined on potassium chloride pellets. Solutions were evaporated under reduced pressure. The light petroleum had b. p. 80—100°.

Acetochloroglucosamine (II).—(i) Dry crystalline 2-acetamido-tetra-*O*-acetyl-2-deoxy-β-D-glucose [22] was shaken with acetic anhydride (30 ml.) saturated at 0° with dry hydrogen chloride. After dissolution was complete the mixture was set aside for 16 hr. at room temperature. It was added to chloroform (125 ml.), cooled, and extracted twice with cold saturated sodium hydrogen carbonate solution, and twice with cold water. The chloroform layer was dried ($MgSO_4$) and evaporated to a syrup which crystallised. The residue was triturated with dry ether and the solid filtered off, to give acetochloroglucosamine, m. p. 126—127° (6·5 g., 69%).

The product recrystallised when dissolved in warm ethyl acetate, treated with light petroleum to turbidity, and kept cold overnight. It then decomposed at 133—134° and had $[\alpha]_D^{18}$ +118° (*c* 1 in $CHCl_3$) (Found: C, 46·1; H, 5·3; N, 3·7; Cl, 9·7. Calc. for $C_{14}H_{20}O_8NCl$: C, 46·0; H, 5·5; N, 3·8: Cl, 9·7%).

(ii) The crystalline α-penta-acetyl compound [prepared by acetylation of the salt (III)] (5 g.) was kept in acetic anhydride (15 ml.) saturated at 0° with dry hydrogen chloride for 16 hr. at room temperature. The solution was cooled to 0°, re-saturated with dry hydrogen chloride,

[20] Bertho and Koziollek, *Chem. Ber.*, 1954, **87**, 934.
[21] Rydon and Smith, *Nature*, 1952, **169**, 922.
[22] Levene, "Hexosamines and Mucoproteins," Longmans, Green & Co., London, 1925.

set aside for 3 days at room temperature, and worked up as above, to give 70% of acetochloroglucosamine identical with that obtained as in (i). Procedure (ii) is necessary for the preparation of the compound (II) from the mixed penta-acetates.[25]

Acetochloroglucosamine is soluble in chloroform, acetone, acetic acid, or nitromethane but insoluble in ether or cold water. The infrared spectrum (Table 1) includes bands at 3250 (banded absorption of secondary amides in the solid state), 1640 (carbonyl absorption of monosubstituted amides), 1540 (CO·NHR), and 755 cm.$^{-1}$ (sharp) (C$^-$Hal stretching).

2-Acetamido-1 : 3 : 4 : 6-tetra-O-acetyl-2-deoxy-β-D-glucopyranose (I).—Acetochloroglucosamine (0·5 g.) was shaken with dry acetic acid (10 ml.) for 16 hr. in the absence of light with silver carbonate (0·5 g.). The silver salts were filtered off and the filtrate was evaporated under reduced pressure. Recrystallisation of the residue from ethanol gave the penta-acetyl derivative (0·31 g., 58%), m. p. 187°, $[\alpha]_D^{20}$ +1·0° (*c* 1 in $CHCl_3$), which did not depress the m. p. of an authentic sample.[18]

Ethyl 2-Acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucoside.—Anhydrous ethanol (125 ml.) was shaken with silver carbonate (5 g.) and anhydrous calcium sulphate (5 g.). After 30 min., crystalline acetochloroglucosamine (5 g.) was added and the mixture shaken for 16 hr. with the exclusion of light, then filtered. The filtrate was evaporated to dryness, the residue dissolved in chloroform (100 ml.) and shaken twice with cold 2% aqueous ammonia and twice with water, and the solution dried, and evaporated to dryness. The residue recrystallised from ethanol, to give *ethyl 2-acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucoside*, m. p. 167° (2·6 g., 51%), $[\alpha]_D^{16\cdot5}$ −24·1° (*c* 1 in MeOH) (Found: C, 51·1; H, 6·7; N, 3·7. $C_{16}H_{25}O_9N$ requires C, 51·2; H, 6·7; N, 3·7%).

Treatment with methanolic ammonia [6] gave a crude product which on chromatography in solvent (*a*) gave spots of R_P 0·57 and 0·45 which correspond respectively to those of the ethyl 2-acetamido-2-deoxy-α- and -β-D-glucoside. Recrystallisation of the crude product from ethanol gave the β-*anomer*, m. p. 178°, $[\alpha]_D^{20}$ −48·9° (*c* 1 in H_2O) (Found: C, 48·9; H, 7·8; N, 5·6. $C_{10}H_{19}O_6N$ requires C, 48·2; H, 7·7; N, 5·5%).

Methyl 2-acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucoside, prepared similarly (42% yield), had m. p. 163°, $[\alpha]_D^{16\cdot5}$ −22·2° (*c* 1 in MeOH) (Found: C, 49·9; H, 6·1; N, 3·8. $C_{15}H_{23}O_9N$ requires C, 49·9; H, 6·3; N, 3·9%), and gave *methyl 2-acetamido-2-deoxy-β-D-glucoside*, m. p. 204° (from ethanol), $[\alpha]_D^{19}$ −47·1° (*c* 1·5 in H_2O) (Found: C, 45·8; H, 7·5; N, 6·1. $C_9H_{17}O_6N$ requires C, 46·0; H, 7·3; N, 6·0%).

Phenyl 2-Acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucoside.—(i) Phenol (5 g.) and acetochloroglucosamine (5 g.) in cold acetone (105 ml.) were treated with 3·3% aqueous sodium hydroxide (45 ml.) and kept for 6 hr. at room temperature and overnight at 5°. The acetone was removed at room temperature and the products were shaken with chloroform (100 ml.). The chloroform layer was extracted with cold dilute alkali and with water, dried, and evaporated *in vacuo*. The residue was recrystallised from propan-2-ol, to give the *phenyl glycoside* (1·8 g., 32%), m. p. 204°, $[\alpha]_D^{18}$ −14·5° (*c* 1 in acetone) (Found: C, 57·5; H, 6·1; N, 3·3. $C_{20}H_{25}O_9N$ requires C, 56·7; H, 5·9; N, 3·3%).

(ii) Phenol (0·66 g.) was melted with mercuric cyanide (0·48 g.), acetochloroglucosamine (1 g.) was added, and the melt heated at 100° for 1 hr. with the exclusion of moisture. The product was dissolved in chloroform (20 ml.), extracted with water, dilute alkali, and water. After drying, the chloroform layer was evaporated and the residue recrystallised from propan-2-ol, to give the phenyl glycoside (150 mg., 13%), m. p. and mixed m. p. 204°, $[\alpha]_D^{20}$ −15·5° (*c* 1 in acetone).

p-Nitrophenyl 2-Acetamido-3 : 4 : 6-tri-O-acetyl-2-deoxy-β-D-glucoside.—*p*-Nitrophenol (5 g.) and acetochloroglucosamine (5 g.) were kept in acetone (105 ml.) and 3·3% aqueous sodium hydroxide (45 ml.) for 6 hr. at room temperature and overnight at 5°. The crystals were filtered off. The acetone was evaporated at room temperature and the solid removed. The combined solids were washed with water and then ether, to give the *glycoside* (2·5 g., 39%). Recrystallisation from 1 : 1 methanol–chloroform gave a product, m. p. 240°, $[\alpha]_D^{18}$ −46·2° (*c* 0·5 in acetone) (Found: C, 51·3; H, 5·1; N, 6·0. $C_{20}H_{24}O_{11}N_2$ requires C, 51·2; H, 5·2; N, 6·0%).

The *o-nitrophenyl analogue*, prepared similarly in 42% yield, had m. p. 196—197° (from ethanol), $[\alpha]_D^{23}$ +3·4° (*c* 1 in acetone) (Found: C, 50·9; H, 5·0; N, 5·7%).

The *p-acetylphenyl analogue* (55% yield) had m. p. 219—220° (from water), $[\alpha]_D^{22}$ −14·6°

[25] Lobry de Bruyn and Van Eckenstein, *Rec. Trav. chim.*, 1899, **18**, 83.

(*c* 0·5 in acetone) (Found: C, 56·8; H, 5·8; N, 2·9. $C_{22}H_{27}O_{10}N$ requires C, 56·8; H, 5·8; N, 3·0%).

The 1-*naphthyl analogue* was obtained similarly. After evaporation of the reaction mixture the products were treated with ether (50 ml.). The solid was filtered off and washed with water and then ether to give a 23% yield. Recrystallisation from propan-2-ol gave a product, m. p. 210—211°, $[\alpha]_D^{21}$ −80·0° (*c* 0·5 in acetone) (Found: C, 60·6; H, 5·8; N, 2·7. $C_{24}H_{27}O_9N$ requires C, 60·9; H, 5·7; N, 2·9%).

Table 2 records removal of the *O*-acetyl groups from the aryl compounds.

1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-2-*amino*-2-*deoxy*-α-D-*glucose Hydrochloride* (III).—Acetochloroglucosamine (3·5 g.) was kept in nitromethane (25 ml.) containing 2N-hydrochloric acid (0·025 ml.) overnight; the white needles were then filtered off, water (0·025 ml.) was added, and the procedure repeated until no further product crystallised out. The *hydrochloride* (3·1 g., 85%), recrystallised from acetic acid, decomposed at 160—186° and had $[\alpha]_D^{22}$ +141° (*c* 1 in H_2O) (Found: C, 44·3; H, 5·7; N, 3·7; Cl, 9·1. $C_{14}H_{22}O_9NCl$ requires C, 43·9; H, 5·5; N, 3·7; Cl, 9·2%). It is soluble in water and acetic acid but insoluble in most other organic solvents including chloroform and nitromethane.

The infrared spectrum (Table 1) shows a complicated set of partly unresolved bands between 3000 and 2500 cm.$^{-1}$, corresponding to reports that amino-acid hydrochlorides show an almost continuous series of bands between 3300 and 2500 cm.$^{-1}$. A small band at 2015 cm.$^{-1}$ is in the position where many hydrochlorides absorb, and the double peaks at 1595 and 1580 cm.$^{-1}$ are found in amino-acid hydrochlorides containing NH_3^+.

2-*Acetamido*-1 : 3 : 4 : 6-*tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucose* (VII).—The salt (III) (5 g.) was kept in pyridine (50 ml.) and acetic anhydride (12·5 ml.) overnight. The mixture was evaporated under reduced pressure and the residue evaporated to dryness several times with absolute methanol. The crystalline residue was dissolved in water (100 ml.) and extracted with chloroform (5 × 15 ml.). The combined chloroform extracts were dried and evaporated to dryness. The residue, recrystallised from ethyl acetate–light petroleum, gave compound (VII), m. p. and mixed m. p. 134—135°, $[\alpha]_D^{21}$ +94° (*c* 1 in $CHCl_3$) (4·2 g., 86%).

1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-2-*amino*-2-*deoxy*-α-D-*glucose* (IX).—The salt (III) (2·1 g.) was shaken in the absence of light for 6 hr. with dry chloroform (50 ml.), anhydrous calcium sulphate (2 g.), and silver carbonate (3 g.), then filtered, and the filtrate was evaporated to dryness at 37°. The crystalline residue was dissolved in warm ethyl acetate (5 ml.) and centrifuged and the supernatant liquid was treated with light petroleum to turbidity and left at 5° overnight, to give the 2-*amino-compound* (1·5 g., 79%). A further recrystallisation gave a product having m. p. 119°, $[\alpha]_D^{20}$ +145·2° (*c* 1 in $CHCl_3$) (Found: C, 48·3; H, 6·1; N, 3·9. $C_{14}H_{31}O_9N$ requires C, 48·4; H, 6·1; N, 4·0%).

2-*Acetamido*-3 : 4 : 6-*tri*-O-*acetyl*-1 : 2-*dideoxy*-1-p-*toluidino*-D-*glucose* (X).—The salt (III) (1·1 g.) was shaken for 24 hr. with *p*-toluidine (0·96 g.) in chloroform (120 ml.), then set aside for several days. Toluidine hydrochloride separated and was filtered off; the brownish filtrate was evaporated to dryness and the semicrystalline residue washed with ether to give the *product* (0·68 g., 54%) which, recrystallised from ethanol, had m. p. 182—183° (decomp.), $[\alpha]_D^{20}$ −38·8° (*c* 1 in $CHCl_3$) (Found: C, 56·9; H, 6·8; N, 6·2. $C_{21}H_{28}O_8N_2$ requires C, 57·7; H, 6·5; N, 6·4%). This product with sodium methoxide [20] gave 2-acetamido-1 : 2-dideoxy-1-*p*-toluidino-D-glucose, $[\alpha]_D^{20}$ −9·5° ⟶ + 2·0° in 6 hr. (*c* 1 in H_2O), decomp. 193°. On chromatography in solvents (*a*) and (*b*) this compound gave spots of R_F 0·74 and 0·63 respectively, identical with those of the compound synthesised from 2-acetamido-2-deoxyglucose and *p*-toluidine.[20]

2-*Acetamido*-3 : 4 : 6-*tri*-O-*acetyl*-2-*deoxy*-α-D-*glucose* (IV).—(i) The salt (III) (2·68 g.) and anhydrous sodium acetate (1 g.) were heated in water (50 ml.) at 65° for 6 hr. and, after cooling, extracted with chloroform (6 × 25 ml.). The combined chloroform extracts were dried (Drierite) and evaporated at 30°. The resulting syrup was dissolved, with slight warming, in anhydrous ether (75 ml.) and kept at −20° overnight. The ether was decanted from the white crystals (which are very deliquescent at this stage), and the flask and contents were dried *in vacuo* over sulphuric acid. The *product* (1·1 g., 45%) softened and melted at 65—75° and had $[\alpha]_D^{20}$ +49·4° (*c* 2·1 in $CHCl_3$), +50·4° ⟶ +26·9° in 4 hr. (*c* 0·5 in H_2O) (Found: C, 47·3, 48·0; H, 6·3, 6·1; N, 4·1, 4·0. $C_{14}H_{31}O_9N$ requires C, 48·4; H, 6·1; N, 4·0%).

(ii) The salt (III) (2·68 g.) and anhydrous sodium acetate (1 g.) were left in water (50 ml.) at room temperature. α (in a 1 dm. tube) of this solution fell in 4 days to a constant value of

XUM

+1·41° which corresponds to $[\alpha]_D^{20}$ +26·7° [assuming the transformation (III) ⟶ (IV)]. The solution was extracted as before and the above product isolated. This product was a white, slightly hygroscopic powder which was very soluble in water or chloroform, moderately soluble in ether, and gave a weak colour with Ehrlich's reagent: 10 mg. of the product in water (0·5 ml.) was mixed with acetic acid (4 ml.) and a 2% solution (0·5 ml.) of *p*-dimethylaminobenzaldehyde in acetic acid containing 2% v/v of 10N-hydrochloric acid; a colour developed which deepened during 48 hr.; then the solution had absorption max. at 540 (ε 206) and 580 mμ (ε 209).

The infrared spectrum (Table 1) shows bands at 3300 (intense) (NH and/or OH), and 1660 and 1540 cm.$^{-1}$ (secondary amide).

2-*Acetamido*-1 : 3 : 4 : 6-*tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucose* (VII).—The compound (IV) (0·2 g.), with pyridine and acetic anhydride,[7] gave a penta-acetyl derivative (60% yield) identical in m. p. and [α] with an authentic sample.

2-*Acetamido*-3 : 4 : 6-*tri*-O-*acetyl*-2-*deoxy*-1-O-(3 : 5-*dinitrobenzoyl*)-α-D-*glucose* (VIII).—The compound (IV) (1 g.) with pyridine and 3 : 5-dinitrobenzoyl chloride [4] gave the product (VIII) (15%), m. p. 172—173°, $[\alpha]_D^{20}$ +94·4° (*c* 1 in $CHCl_3$).

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959. *Synthesis of Some* 1 : 2-*Benzophenanthridines.*

By K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and N. Viswanathan.

Syntheses of 7 : 2′ : 3′- and 6 : 2′ : 3′-trimethoxy-, 7-methoxy-2′ : 3′-methylenedioxy-, and 6-methoxy-2′ : 3′-methylenedioxy-9-methyl-1 : 2-benzophenanthridine (V) are reported.

For work on some 1 : 2-benzophenanthridine alkaloids, we have prepared four new compounds of this group, by a modification of the method of Richardson *et al.*[1]

Reduction of the oxime of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-*p*-methoxyphenyl-1-oxonaphthalene [2] (I*a*) with sodium amalgam and acetylation of the resulting amine yielded the acetamide (II*a*) which on dehydrogenation over palladised charcoal gave a mixture of 6 : 7-dimethoxy-2-*p*-methoxyphenylnaphthalene (IV*a*) and its 1-acetamido-derivative (III*a*), identified by analysis and ultraviolet spectra (Fig. 1). A similar partial removal of the amide group has been observed in the dehydrogenation of 1-acetamido-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxynaphthalene.[3] Cyclisation of the amide (III*a*) with phosphorus oxychloride gave a good yield of 7 : 2′ : 3′-trimethoxy-9-methyl-1 : 2-benzophenanthridine (V*a*). To our knowledge the cyclisations of the amides (III*a* and *c*) (reported below) are the only instances where cyclisation has proceeded *meta* to an alkoxy-group, illustrating the great facility of the Morgan–Walls reaction: [4] Bischler–Napieralski reaction [4] of phenethylamides with alkoxy-groups *meta* to the point of cyclisation either fails or yields only traces of *iso*quinolines.

An attempt to prepare the benzophenanthridine (V*a* but with H in place of Me) was unsuccessful because, although a Leuckart reaction with the tetralone (I*a*) gave a satisfactory yield of the formamide analogous to (II*a*), dehydrogenation of the latter gave only the naphthalene (IV*a*) and not the desired formamide analogous to (III*a*).

Addition of hydrogen cyanide to 3 : 3′ : 4′-trimethoxychalkone (VI*b*) gave the keto-nitrile (VII*b*), which was hydrolysed in two steps to the benzoylpropionic acid (VIII*b*).

[1] Richardson, Robinson, and Seijo, *J.*, 1937, 835.
[2] Golberg and Robinson, *J.*, 1941, 575.
[3] Govindachari and Arumugam, *J.*, 1955, 2534.
[4] Whaley and Govindachari, "Organic Reactions," John Wiley & Sons, Inc., 1951, Vol. VI, p. 131.

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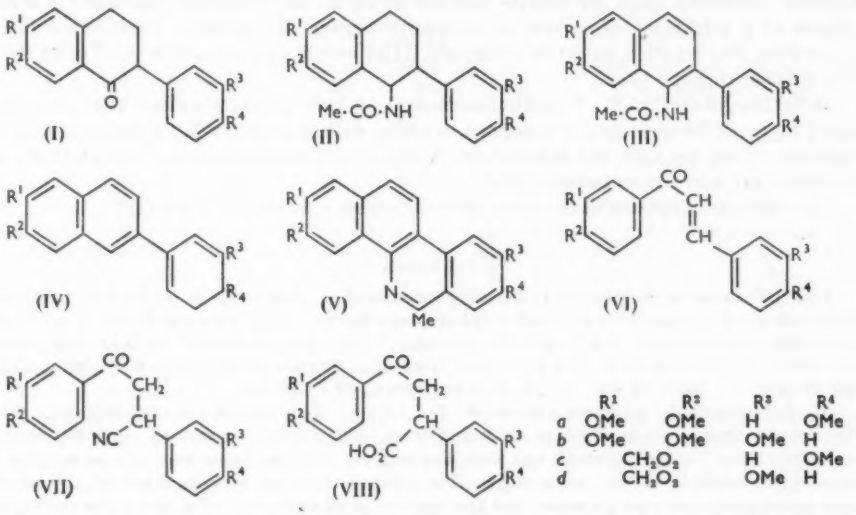
Clemmensen reduction, and cyclisation of the resulting γ-phenylbutyric acid, gave 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-*m*-methoxyphenyl-1-oxonaphthalene (I*b*), converted into the acetamide (II*b*) through its oxime. Dehydrogenation of this amide yielded,

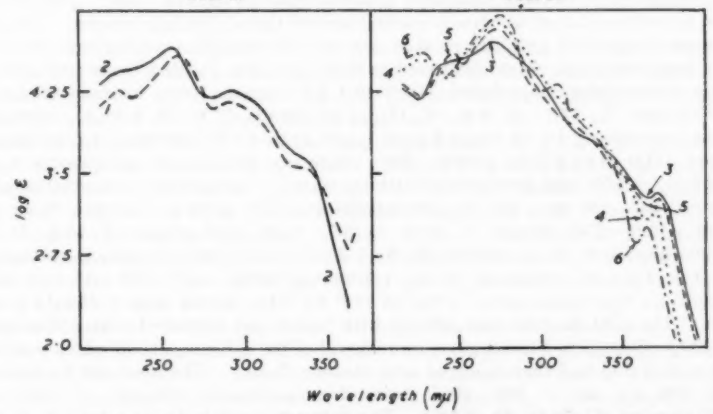


	R¹	R²	R³	R⁴
a	OMe	OMe	H	OMe
b	OMe	OMe	OMe	H
c	CH_2O_2		H	OMe
d	CH_2O_2		OMe	H

as before, a mixture of the naphthalene derivative (IV*b*) and the acetamide (III*b*). Cyclisation of the last compound gave 6 : 2′ : 3′-trimethoxy-9-methyl-1 : 2-benzophenanthridine (V*b*).

Synthesis of 7-methoxy-9-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine (V*c*) was achieved by starting with 4-methoxy-3′ : 4′-methylenedioxychalkone (VI*c*). The

FIG. 1. FIG. 2.



Absorption spectra of (1) 6 : 7-*dimethoxy*-2-p-(IV*a*) *and* (2)-m-*methoxyphenylnaphthalene* (IV*b*) *and* (3) 7 : 2′ : 3′-*trimethoxy-* (V*a*), (4) 6 : 2′ : 3′-*trimethoxy-* (V*b*), (5) 7-*methoxy*-2′ : 3′-*methylenedioxy-* (V*c*), *and* (6) 6-*methoxy*-2′ : 3′-*methylenedioxy-* (V*d*) 9-*methyl*-1 : 2-*benzophenanthridine, all in* EtOH.

acetyl derivative required for preparation of the chalkone was conveniently obtained by the action of dimethylcadmium on piperonoyl chloride. The chalkone (VI*c*) was then converted through the nitrile (VII*c*) into the benzoylpropionic acid (VIII*c*). Reduction

to the phenylbutyric acid for cyclisation to the tetralone (Ic) was found to proceed better by hydrogenation over palladium–charcoal in presence of perchloric acid than by the Clemmensen procedure. As the oxime of the tetralone (Ic) gave only poor yields of the required acetamide (IIc), its acetate was subjected to the Schroeter reaction [5] (for conversion of a tetralone oxime into an α-naphthylamine derivative). Acetylation of the amine from this reaction gave the acetamide (IIIc) which was cyclised in good yield to the benzophenanthridine (Vc).

6-Methoxy-9-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine (V*d*) was prepared by a similar sequence of reactions, starting with 3-methoxy-3′ : 4′-methylenedioxychalkone (VI*d*), through the keto-nitrile (VII*d*), the benzoylpropionic acid (VIII*d*), the tetralone (I*d*), and the acetamide (III*d*).

The ultraviolet spectra of the benzophenanthridines are recorded in Fig. 2.

Experimental

7 : 2′ : 3′-*Trimethoxy*-9-*methyl*-1 : 2-*benzophenanthridine* (V*a*).—(i) 1 : 2 : 3 : 4-*Tetrahydro*-1-*hydroxyimino*-6 : 7-*dimethoxy*-2-p-*methoxyphenylnaphthalene*. The tetralone [2] (I*a*) (1 g.), hydroxylamine hydrochloride (1 g.), and dry pyridine (5 ml.), heated at 100° for 5 hr. and poured into water, yielded the *oxime* (0·9 g.), cubes [from light petroleum (b. p. 40—60°)], m. p. 215—216° (Found: C, 70·3; H, 6·4. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·4%).

(ii) 1-*Acetamido*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-p-*methoxyphenylnaphthalene* (II*a*). The above oxime (1 g.) in absolute alcohol (150 ml.) was reduced at 60—65° with 5% sodium amalgam (150 g.), added in small lots with shaking, the solution being kept almost neutral by intermittent addition of 50% acetic acid. The alcoholic solution was decanted off, the solvent evaporated under reduced pressure, and the residual solid extracted with hot water containing concentrated hydrochloric acid (10 ml.). After filtration, the acid solution was extracted once with benzene, then basified, and the base extracted with benzene. The dried (K_2CO_3) extract was evaporated and the residual oil heated with acetic anhydride (2 ml.) and dry pyridine (0·2 ml.) for 1 hr. at 100°. Addition of water and crystallisation of the precipitate from dilute alcohol yielded the *acetamide* (0·63 g.) as flakes, m. p. 193—195° (Found: C, 70·7; H, 6·7. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

(iii) *The benzophenanthridine* (V*a*). The foregoing amide (0·3 g.) in dry *p*-cymene (50 ml.) was dehydrogenated over 30% palladium–charcoal (0·3 g.) at 240—260°. The solution was filtered hot from the catalyst which was washed several times with hot benzene. The combined extracts were evaporated and the residue was chromatographed on benzene over alumina. The first 3 fractions of the eluate (collected in 5 ml. portions) yielded, on evaporation, 6 : 7-*dimethoxy*-2-p-*methoxyphenylnaphthalene* (IV*a*) (0·1 g.), needles (from benzene–ethanol), m. p. 158—159° (Found: C, 77·7; H, 6·4. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1%). Further elution with benzene containing 1% of ethanol gave 1-acetamido-6 : 7-dimethoxy-2-*p*-methoxyphenylnaphthalene (III*a*) (0·15 g.), m. p. 205—208°, which was heated with phosphorus oxychloride (1 ml.) for 2 hr. at 100° and decomposed with ice-water. Basification of the yellow precipitate with sodium hydroxide gave the *benzophenanthridine* (V*a*) (0·09 g.), needles (from pyridine–ethanol), m. p. 229—230° (Found: C, 75·4; H, 5·7. $C_{21}H_{19}O_3N$ requires C, 75·7; H, 5·7%).

(iv) 1-*Formamido*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-p-*methoxyphenylnaphthalene*. The tetralone (I*a*) (2 g.) in formamide (5 ml.) containing formic acid (0·25 ml.) and ammonium sulphate (0·25 g.) was heated under reflux at 180° for 3 hr., formic acid (0·25 ml.) being added every 1 hr. The cold mixture was diluted with water and extracted with chloroform. The dried (Na_2SO_4) chloroform extract gave, on removal of the solvent, a solid which was triturated with methanol (5 ml.) and then digested with acetone (5 ml.). The insoluble fraction gave the *formamide* (0·6 g.), m. p. 199—200° (from dioxan–ethanol) (Found: C, 71·0; H, 6·5. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7%). The formamide (0·5 g.) was heated in *p*-cymene (50 ml.) with 30% palladium–charcoal: chromatography of the product in benzene over alumina gave only the naphthalene (IV*a*) (0·35 g.), m. p. and mixed m. p. 158—159°.

6 : 2′ : 3′-*Trimethoxy*-9-*methyl*-1 : 2-*benzophenanthridine* (V*b*).—(i) γ-(3 : 4-*Dimethoxyphenyl*)-α-m-*methoxyphenyl*-γ-*oxobutyronitrile* (VII*b*). A mixture of acetoveratrone (20 g.), *m*-methoxybenzaldehyde (15 g.), alcohol (75 ml.), and 10% aqueous sodium hydroxide (20 ml.) was shaken

[5] Schroeter, *Ber.*, 1930, **63**, 1317.

for a few minutes, left overnight, diluted with water and extracted with chloroform. The dried (Na_2SO_4) chloroform extract, on evaporation and distillation, yielded 3 : 3′ : 4′-trimethoxychalkone (VI*b*) (25 g.), b. p. 218—220°/0·08 mm. A solution of the chalkone (25 g.) in boiling methanol (70 ml.) was treated with sodium cyanide (12 g.) and 3 drops of phenolphthalein, then slowly with acetic acid (5 ml.) and water (25 ml.) at such a rate that the solution remained pink. After boiling for 10 min., the solution was poured into ice. The gummy product, when washed with water, yielded the *nitrile* (VII*b*) (21 g.), pale yellow cubes (from acetone), m. p. 153—154° (Found: C, 70·4; H, 5·3. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·7%).

(ii) *γ-(3 : 4-Dimethoxyphenyl)-α-m-methoxyphenyl-γ-oxobutyric acid* (VIII*b*). A stirred suspension of the above nitrile (20 g.) in glacial acetic acid (100 ml.) was treated with concentrated sulphuric acid (20 ml.) in small lots, kept for 15 min., poured into ice, and extracted with chloroform. The extract was washed with sodium carbonate solution and water, dried (Na_2SO_4), and evaporated. The residual oil was rubbed with methanol and the solid crystallised from the same solvent, to give *γ-(3 : 4-dimethoxyphenyl)-α-m-methoxyphenylbutyramide* (14 g.) as plates, m. p. 129—130° (Found: C, 66·2; H, 6·2. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%). The amide (13 g.) was refluxed in alcohol (50 ml.) and 10% aqueous sodium hydroxide (70 ml.) for 15 hr., diluted with water (120 ml.), and extracted once with chloroform. The aqueous layer, on acidification, yielded the *acid* (10 g.), plates (from dilute alcohol), m. p. 153—154° (Found: C, 66·1; H, 6·2. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%).

(iii) *1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-m-methoxyphenyl-1-oxonaphthalene* (I*b*). The above keto-acid (10 g.), toluene (40 ml.), concentrated hydrochloric acid (53 ml.), zinc amalgam (22 g.), and 5% acetic acid (15 ml.) were refluxed for 48 hr., concentrated hydrochloric acid (10 ml.) being added every 10 hr. The toluene layer was separated, the aqueous layer was extracted once with benzene and the combined toluene–benzene extracts were shaken with sodium carbonate solution. Acidification of the aqueous layer, followed by extraction with chloroform, gave *α-m*-methoxyphenyl-*γ*-(3 : 4-dimethoxyphenyl)butyric acid (8 g.) as a pale yellow oil. This was refluxed with phosphorus oxychloride (15 ml.) for 5 min. and the red solution poured on ice. The pink precipitate was filtered off, washed with sodium carbonate solution and water, dried, and chromatographed in benzene over alumina, the eluate being collected in 10 ml. fractions. The 3 initial fractions gave a substance, m. p. 112—114° (from methanol) (Found: C, 69·0; H, 5·6%). Later fractions gave the *tetralone* (I*b*) (4 g.), plates (from methanol), m. p. 143—145° (Found: C, 73·4; H, 6·2. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%), yielding an *oxime* (pyridine method) as cubes [from benzene–light petroleum (b. p. 40—60°)], m. p. 173—175° (Found: C, 69·6; H, 6·6%).

(iv) *1-Acetamido-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-m-methoxyphenylnaphthalene* (II*b*). The above oxime (2 g.) in absolute alcohol (150 ml.) was reduced with 5% sodium amalgam (300 g.), and the product worked up as above, yielding the *acetamide* (1·2 g.) as needles (from dilute alcohol), m. p. 172—173° (Found: C, 71·6; H, 7·1%).

(v) *The benzophenanthridine* (V*b*). The foregoing acetamide (1·2 g.) in *p*-cymene (70 ml.), dehydrogenated over 30% palladium–charcoal (0·8 g.) at 230—250° and chromatographed in benzene over alumina, yielded in the initial fractions *6 : 7-dimethoxy-2-m-methoxyphenylnaphthalene* (IV*b*) (0·5 g.), needles (from methanol), m. p. 129—130° (Found: C, 77·7; H, 6·1%). Elution with benzene containing ethanol gave 1-acetamido-6 : 7-dimethoxy-2-*m*-methoxyphenylnaphthalene (III*b*) (0·6 g.) as a gum which was cyclised with phosphorus oxychloride (3 ml.) to the *benzophenanthridine* (V*b*) (0·4 g.), needles (from pyridine–ethanol), m. p. 183—185° (Found: C, 75·2; H, 5·5%).

7-Methoxy-9-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine (V*c*).—(i) To an ice-cooled solution of methylmagnesium bromide [from magnesium (9·8 g.) in ether (200 ml.) and excess of methyl bromide] was added, in a nitrogen atmosphere, during 5 min., powdered anhydrous cadmium chloride (38 g.; dried at 110° to constant wt.). Stirring under reflux was continued for 1 hr. After removal of the ether, benzene (60 ml.) was added and an additional 25 ml. of benzene was distilled off. After addition of more solvent (240 ml.), the mixture was cooled to 50° and a solution of piperonoyl chloride [6] (36 g.) in benzene (50 ml.) was added dropwise, considerable heat being evolved. The mixture was refluxed for 1 hr., left overnight, then decomposed with dilute sulphuric acid. The aqueous layer was extracted with more solvent. The combined benzene extracts were washed with sodium carbonate solution and water, dried

[6] Barger, *J.*, 1908, **93**, 567.

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(Na_2SO_4), and evaporated. The residue, on cooling, gave 4-acetyl-1 : 2-methylenedioxybenzene (32 g.) as a pale yellow solid, m. p. and mixed m. p. (with a sample [1] obtained by oxidation of 1-piperonoylethanol) 84—85°.

(ii) 4-*Methoxy*-3′ : 4′-*methylenedioxychalkone* (VI*c*). *p*-Methoxybenzaldehyde (15 g.) with the preceding ketone (18·2 g.) in alcohol (86 ml.) containing 10% aqueous sodium hydroxide (20 ml.) yielded the *chalkone* (28 g.) as pale yellow needles (from methanol), m. p. 142° (Found: C, 72·0; H, 4·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

(iii) α-p-*Methoxyphenyl*-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyronitrile* (VII*c*). A stirred solution of the above chalkone (20·5 g.) in 2-ethoxyethanol (80 ml.) containing acetic acid (4·5 ml.) was treated at 100°, during 3 min., with potassium cyanide (9·3 g.) in water (17 ml.). Heating was continued for a further 10 min. and water (100 ml.) added, to give the *nitrile* (15 g.), pale yellow needles (from alcohol), m. p. 130° (Found: C, 70·3; H, 5·3. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9%).

(iv) α-p-*Methoxyphenyl*-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyric acid* (VIII*c*). The above nitrile (18 g.) in acetic acid (120 ml.) with concentrated sulphuric acid (18 ml.) gave the *amide* (15 g.), needles (from methanol), m. p. 169° (Found: C, 66·3; H, 5·3. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2%), which with 7% aqueous sodium hydroxide (200 ml.) and alcohol (80 ml.) gave in 6 hr. the *acid* (VIII*b*) (12·5 g.), needles (from methanol), m. p. 169° (Found: C, 65·6; H, 5·4. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%).

(v) 1 : 2 : 3 : 4-*Tetrahydro*-2-p-*methoxyphenyl*-6 : 7-*methylenedioxy*-1-*oxonaphthalene* (I*c*). The above keto-acid (2·5 g.) in acetic acid (20 ml.) containing 70% perchloric acid (0·5 ml.) was reduced at 60° with hydrogen at 1 atm. in presence of 5% palladium–charcoal (0·5 g.) during 1 hr. The catalyst was filtered off and washed with acetic acid. After removal of the solvent *in vacuo*, the residue was extracted with chloroform. The chloroform was washed with water, dried (Na_2SO_4), and evaporated, to yield α-*p*-methoxyphenyl-γ-(3 : 4-methylenedioxyphenyl)-butyric acid as a yellow oil (2 g.) which with boiling phosphorus oxychloride (5 ml.) for 5 min. yielded as the single product the *tetralone* (I*c*) (1·5 g.), pale yellow prisms (from methanol), m. p. 144—145° (Found: C, 72·6; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). Clemmensen reduction of the keto-acid (2·5 g.) and cyclisation with phosphorus oxychloride gave only 0·8 g. of the tetralone. The *oxime* (0·8 g. from 1 g. of the tetralone; pyridine method) formed needles (from alcohol), m. p. 160° (Found: C, 69·3; H, 5·7. $C_{18}H_{17}O_4N$ requires C, 69·5; H, 5·5%), and gave, with acetic anhydride (1·2 ml.) in pyridine (1 ml.) at 100°, the *acetate* (0·8 g.), needles (from alcohol), m. p. 151—152° (Found: C, 68·1; H, 5·4; N, 4·3. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4; N, 4·0%).

(vi) 1-*Acetamido*-1 : 2 : 3 : 4-*tetrahydro*-2-p-*methoxyphenyl*-6 : 7-*methylenedioxynaphthalene* (II*c*). The oxime (1 g.) in absolute ethanol (150 ml.) was reduced at 60—65° with sodium amalgam (150 g.), to the *acetamide* (0·2 g.), needles (from dilute alcohol), m. p. 191—192° (Found: C, 71·3; H, 6·4. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%).

(vii) *The phenanthridine* (V*c*). A solution of the oxime acetate (0·5 g.) in acetic acid (5 ml.) and acetic anhydride (1·5 ml.) was saturated with dry hydrogen chloride at 0° and heated at 90—95° in a sealed tube for 8 hr., then decomposed with water. The yellow solid obtained was dissolved in hot water and filtered. The filtrate was extracted with benzene, basified with sodium hydroxide, and again extracted with benzene. The final, dried (Na_2SO_4) benzene solution yielded a yellow oil (0·25 g.) which with acetic anhydride (1 ml.) and pyridine (0·5 ml.) at 100° gave 1-acetamido-2-(*p*-methoxyphenyl)-6 : 7-methylenedioxynaphthalene (III*c*) (0·25 g.), m. p. 166—169°, cyclised with phosphorus oxychloride (2·5 ml.) at 100° to the *phenanthridine* (V*c*) (0·12 g.), needles (from pyridine–ethanol), m. p. 185—186° (Found: C, 75·9; H, 5·0. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·7%).

6-*Methoxy*-9-*methyl*-2′ : 3′-*methylenedioxy*-1 : 2-*benzophenanthridine* (V*d*).—(i) 3-*Methoxy*-3′ : 4′-*methylenedioxychalkone* (VI*d*). A mixture of *m*-methoxybenzaldehyde (7·5 g.), 4-acetyl-1 : 2-methylenedioxybenzene (9·1 g.), alcohol (43 ml.), and 10% aqueous sodium hydroxide (10 ml.) gave the *chalkone* (14 g.), pale yellow needles (from alcohol), m. p. 100° (Found: C, 72·0; H, 4·9%).

(ii) α-m-*Methoxyphenyl*-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyronitrile* (VII*d*). The foregoing chalkone (10 g.) in 2-ethoxyethanol (45 ml.) containing glacial acetic acid (5·25 ml.) was treated with potassium cyanide (4·65 g.) in water (8·5 ml.), yielding the *nitrile* (9 g.), needles (from dilute acetic acid), m. p. 76—77° (Found: C, 69·6; H, 4·9%).

(iii) α-m-*Methoxyphenyl*-γ-(3 : 4-*methylenedioxyphenyl*)-γ-*oxobutyric acid* (VIII*d*). The

foregoing nitrile (9 g.) in acetic acid (45 ml.) was treated with concentrated sulphuric acid (7·5 ml.), to yield the *amide* (8·5 g.), needles (from methanol), m. p. 140° (Found: C, 65·7; H, 4·8%). The amide (7·5 g.) in alcohol (45 ml.) and 7% aqueous sodium hydroxide (90 ml.), refluxed for 5 hr., yielded the *acid* (6·5 g.), needles (from dilute alcohol), m. p. 145° (Found: C, 65·7; H, 5·2%).

(iv) 1 : 2 : 3 : 4-*Tetrahydro*-2-m-*methoxyphenyl*-6 : 7-*methylenedioxy*-1-*oxonaphthalene* (I*d*). The above acid (2 g.) in acetic acid (15 ml.) containing 70% perchloric acid (0·5 ml.) was reduced at 1 atm. over 5% palladised charcoal (0·5 g.) to α-*m*-methoxyphenyl-γ-(3 : 4-methylenedioxyphenyl)butyric acid (1·8 g.), a yellow oil. With phosphorus oxychloride at 100° (15 min.) this gave, after chromatography in benzene over alumina, the *tetralone* (I*d*) (0·7 g.), prisms (from alcohol), m. p. 98—99° (Found: C, 72·8; H, 5·5%). The *oxime* (0·8 g. from 1 g. of the tetralone; pyridine method) formed needles (from alcohol), m. p. 164—165° (Found: C, 69·3; H, 5·6%), and with acetic anhydride and pyridine at 100° gave an *acetate* (0·6 g.), needles (from alcohol), m. p. 132—133° (Found: C, 67·7; H, 5·5%).

(v) *The phenanthridine* (V*d*). The foregoing oxime acetate (0·4 g.) in acetic acid (4 ml.) and acetic anhydride (1·5 ml.) was saturated with hydrogen chloride at 0° and heated at 90—95° in a sealed tube for 8 hr., yielding a brownish oily base, which, with acetic anhydride (1·5 ml.) and pyridine (0·5 ml.) at 100° yielded a dark brown gum. Chromatography in benzene over alumina yielded 1-acetamido-2-*m*-methoxyphenyl-6 : 7-methylenedioxynaphthalene (III*d*) (0·06 g.), cyclised with phosphorus oxychloride (1 ml.) to the *phenanthridine* (0·04 g.), pale yellow needles (from pyridine–ethanol), m. p. 197—198° (Found: C, 76·0; H, 4·7%).

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960. *Aspects of Stereochemistry. Part IX.* The Formation of Fluorohydrins from the Cholesteryl 5 : 6-Epoxides and Boron Trifluoride–Ether Complex.*

By H. B. HENBEST and T. I. WRIGLEY.

Whereas 6-ketones were the only crystalline products obtained from the reaction of unsubstituted 5 : 6-epoxysteroids with boron trifluoride–ether complex, the presence of substituents (acetoxy, chloro) at $C_{(3)}$ can cause diaxial fluorohydrins to be formed in good yields. The results are discussed in terms of the conformational and electrical effects of the nearby $C_{(3)}$-substituents.

IN our previous paper on this topic,[1] reactions of boron trifluoride–ether complex with some aliphatic tri- and tetra-substituted epoxides of the steroid series were described, and the α- and β-5 : 6-epoxides were shown to yield 6-ketones by stereospecific hydrogen shifts. For the investigation of the effect of nearby groups on these reactions, the 3-substituted 5 : 6-epoxides were the obvious choice.

5α : 6α-*Epoxides.*—The following Table summarises the products obtained from various 5α : 6α-epoxides.

$C_{(3)}$ substituent	"Non-polar material"	6-Oxocoprostanes	Hydroxy-compounds
3α-OAc	—	Ketone (61%)	Oil (18%)
H	Oil (37%)	Ketone (34%)	Oil (20%)
3β-OAc	—	†	Fluorohydrin (74%) *
3β-Cl	—	†	Fluorohydrin (>45%)

* This yield was obtained (some unchanged material being allowed for) with a reaction time of 5 min. Longer reaction times caused the yield to fall: 41% (15 min.), 24% (120 min.).
† Although exact figures cannot be given, these yields are less than 5%.

The crystalline products were either 6-oxocoprostanes or diaxial fluorohydrins. The structures of the latter are discussed at the end of the paper.

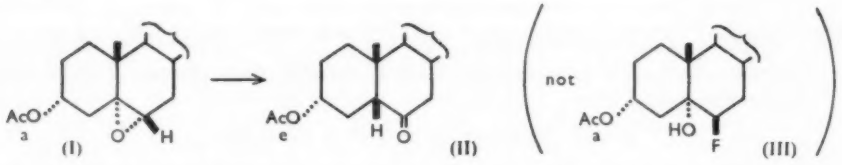
* Part VIII, *J.*, 1957, 4608.

[1] Henbest and Wrigley, *J.*, 1957, 4596.

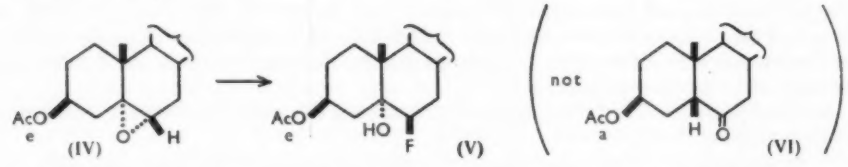
From two of the 3-substituted 5 : 6-epoxides, fluorohydrins are formed instead of a ketone as from the unsubstituted compound. In our earlier paper it was suggested that, in the production of the ketone from the 5 : 6-epoxide, the bond from oxygen to the more alkylated $C_{(5)}$-position was appreciably ionized in the transition state. As intramolecular electron-attracting groups have been shown [2,3] to slow down the rate of S_N solvolyses, the ionization necessary for the formation of 6-ketones from the epoxides containing acetoxy- or chloro-groups at $C_{(3)}$ may similarly be inhibited. The alternative reaction leading to fluorohydrin can then operate, this type of reaction involving dual attack of the Lewis acid and an external fluoride nucleophil. In accord with this picture, the configurations of the fluorohydrins are diaxial and they are formed at slower rates than are the 6-ketones from the unsubstituted epoxides. However, the mechanistic picture is not complete in that the precise origin and/or mode of attack of the fluoride nucleophil and the nature of the initial reaction product [? $\rangle CF{\cdot}C(OBF_2)\langle$] have yet to be determined.

The second factor required to explain the present results is that reactions leading to less favourable molecular conformations are prohibited. The reactions will be discussed in terms of these electrical and conformational factors.

Compared with the unsubstituted 5α : 6α-epoxide, the 3α-acetoxy-compound (I) gave a higher yield of a 6-ketone (*i.e.* II), the reaction being assisted by the change of the acetate conformation from axial (a) to equatorial (e). However, the rate of reaction of the substituted epoxide was slower, in line with the general suggestion that ionization of the $C_{(5)}$–O bond would be more difficult. Formation of the diaxial fluorohydrin (III) is probably discouraged because increase of compression (of 3α- and 5α-axial substituents) would be involved.



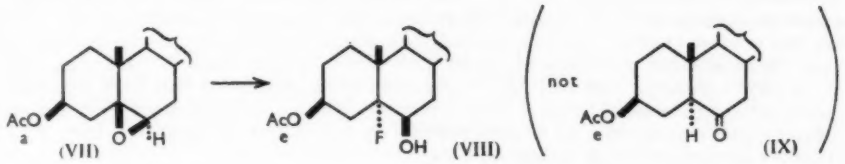
In contrast, the 3β-acetoxy-epoxide (IV) gave very little ketone (*i.e.* VI), the fluorohydrin (V) being the major product. In this case, formation of a ketone is inhibited for both conformational and electrical reasons. Similarly, the 3β-chloro-analogue of (IV) also gave a fluorohydrin, the infrared absorption of the total reaction product showing that very little ketone was produced.



5β : 6β-*Epoxides.*—The reactions of only two compounds have been studied but here again the introduction of an acetoxy-substituent at $C_{(3)}$ profoundly alters the course of reaction. Thus, whereas the unsubstituted 5β : 6β-epoxide afforded a 6-ketone (cholestan-6-one), the diaxial fluorohydrin (VIII) was obtained from the 3β-acetoxy-compound (VII). Formation of either the fluorohydrin (VIII) or the ketone (IX) can derive assistance from the change of acetate conformation from axial to equatorial, and so the difficulty in ionizing the $C_{(5)}$–O bond, necessary for the production of the ketone (IX), is decisive in this case. The rate of reaction of the substituted epoxide (VII) was slower than that of the

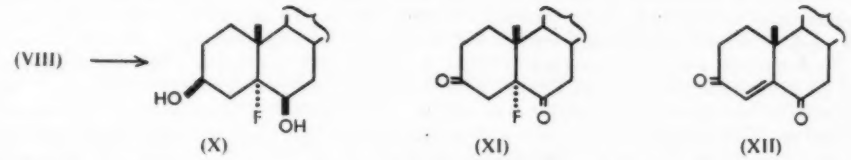
[1] Brown, Kharasch, and Chao, *J. Amer. Chem. Soc.*, 1940, **62**, 3435.
[2] Streitwieser, jun., *ibid.*, 1956, **78**, 4935.

unsubstituted compound, agreeing with the general suggestion that the slower reaction leading to a fluorohydrin becomes of importance only when the normally more rapid ionization-hydrogen shift reaction is inhibited.



Structures of Reaction Products.—Apart from the usual evidence, the proof of structure of the 5β-6-ketone (II) followed from its epimerisation by alkali to the known 5α-6-ketone.

The hydroxyl group (infrared evidence) in the fluorohydrin (V) was resistant to normal



acetylation and therefore was 5α- in configuration. The *trans*-arrangement of $C_{(5)}$ and $C_{(6)}$ substituents was confirmed by treatment of the fluorohydrin with potassium *tert.*-butoxide whereupon the initial α-epoxide formed. The rotation of the fluorohydrin was also similar to that of the related known chlorohydrin. [This fluorohydrin is unusual in that its infrared spectrum contained a second (weaker) carbonyl band at 1713 cm.$^{-1}$ in addition to the usual acetate band at 1733 cm.$^{-1}$. Experiments (to be reported later) have shown that the new band arises from appreciable intermolecular association.]

The presence of a secondary hydroxyl group in the fluorohydrin (VIII) was demonstrated by acetylation and oxidation, and the *trans*-disposition of groups by the formation of cholesterol β-epoxide on treatment with alkali. The 3 : 6-diol (X) was best prepared by reductive hydrolysis of the acetate (VIII) with lithium aluminium hydride. Oxidation of the diol gave the diketone (XI) from which hydrogen fluoride was eliminated on treatment with alumina to yield the known cholest-4-ene-3 : 6-dione (XII).

The presence of fluorine in the fluorohydrins (V) and (VIII) was confirmed by elemental analyses. These were determined at the University of Birmingham by arrangement with Professor M. Stacey, whom we thank.

Experimental

General directions are as given before.[1]

3α-Acetoxycoprostan-6-one (II).—A solution of 3α-acetoxy-5α : 6α-epoxycholestane (1·93 g.) and boron trifluoride–ether complex (1·4 c.c.) in benzene (31 c.c.) was kept at 20° for 14 hr. The product was isolated with benzene and chromatographed on deactivated alumina (125 g.). Elution with benzene gave *3α-acetoxycoprostan-6-one* (1·24 g.; 61%), m. p. 142—143° (from methanol), $[\alpha]_D$ −21° (Found: C, 78·1; H, 10·75. $C_{29}H_{48}O_3$ requires C, 78·35; H, 10·9%). Infrared absorption (in CS_2): carbonyl peaks at 1733 (acetate) and 1703 cm.$^{-1}$ (6-ketone). Elution with ether–benzene (1 : 3) gave an oil (0·28 g.; 18%) which showed hydroxyl absorption in the infrared region.

A similar experiment, with only 5 min. reaction time, gave starting material (20%), the 6-ketone (37%), and the non-crystalline hydroxy-compound (15%).

3α-Acetoxycoprostan-6-one (76 mg.) in benzene (3 c.c.) was adsorbed on to alumina (5 g.) impregnated with potassium hydroxide. After 16 hr. the steroid was eluted with ether to give

3α-hydroxycholestan-6-one (67 mg.), m. p. 157—159° (from aqueous methanol), $[\alpha]_D$ 0°. Acetylation gave the 3α-acetate, m. p. 102—105° (from aqueous acetone), $[\alpha]_D$ −10°. (Lit. values for the alcohol, m. p. 159—160°, $[\alpha]_D$ +3°; for the acetate, m. p. 107—108°, $[\alpha]_D$ −4°.)

3β-*Acetoxy*-6β-*fluorocholestan*-5α-*ol* (V).—Boron trifluoride–ether complex (0·9 c.c.) was added to a solution of 3β-acetoxy-5α : 6α-epoxycholestane (1·12 g.) in benzene (20 c.c.) at 20°. After 5 min. the product (1·08 g.) was isolated and then chromatographed on deactivated alumina (30 g.). Benzene–light petroleum (1 : 1, 80 c.c.) eluted starting material (161 mg., 18%), m. p. 94—97°. Benzene (200 c.c.) eluted 3β-*acetoxy*-6β-*fluorocholestan*-5α-*ol* (638 mg., 62%); elution with benzene–ether (9 : 1) gave gummy material (20%). Crystallisation from methanol afforded the pure fluorohydrin, m. p. 207—209°, $[\alpha]_D$ −21° (Found: C, 74·75; H, 10·8; F, 4·0. $C_{29}H_{49}O_2F$ requires C, 75·0; H, 10·55; F, 4·3%).

Prolongation of the reaction time caused the solution to become blue and the yield of fluorohydrin obtained by chromatography to fall (see Table).

The fluorohydrin was recovered from treatment with acetic anhydride and pyridine at 20° for 24 hr. Solutions of the fluorohydrin (175 mg.) in *tert.*-butyl alcohol (12 c.c.) and N-potassium *tert.*-butoxide in *tert.*-butyl alcohol (4 c.c.) were mixed and then kept at 20° for 16 hr. Crystallisation from methanol gave 5α : 6α-epoxycholestan-3β-ol (110 mg.), m. p. and mixed m. p. 140—141°; infrared absorption identical with that of an authentic sample.

3β-*Acetoxy*-5α-*fluorocholestan*-6β-*ol* (VIII).—A solution of 3β-acetoxy-5β : 6β-epoxycholestane (0·9 g.) in benzene (25 c.c.) was treated with boron trifluoride–ether complex (0·4 c.c.). The reaction (followed polarimetrically) was completed in 30 min. and the product was then isolated with ether. The solution in hot methanol was filtered to remove some sparingly soluble material (60 mg.) and cooled to give the *fluorohydrin* (0·69 g.), m. p. 160—170°. The pure compound had m. p. 171—172°, $[\alpha]_D$ −9° (Found: C, 74·9; H, 10·65; F, 4·05. $C_{29}H_{49}O_2F$ requires C, 75·0; H, 10·55; F, 4·3%). Treatment of the compound with alkali, as described for the previous fluorohydrin, gave 5β : 6β-epoxycholestan-3β-ol, m. p. and mixed m. p. 131—133°.

Acetylation of the fluorohydrin at 20° gave 3β : 6β-*diacetoxy*-5α-*fluorocholestane*, double m. p. 124—125°, 160—161°, $[\alpha]_D$ −20° (Found: C, 73·6; H, 10·2. $C_{31}H_{51}O_4F$ requires C, 73·5; H, 10·1%).

The fluorohydrin (0·9 g.) in acetone (40 c.c.) was oxidised with 8N-chromic acid. The product was isolated with ether and chromatographed on deactivated alumina (25 g.). Light petroleum eluted 3β-*acetoxy*-5α-*fluorocholestan*-6-*one* (0·79 g.), m. p. 122—124° (from methanol), $[\alpha]_D$ −1° (Found: C, 75·5; H, 10·35. $C_{29}H_{47}O_3F$ requires C, 75·4; H, 10·15%): infrared absorption (in CS_2), carbonyl bands at 1735 (acetate) and 1703 cm.$^{-1}$ (6-ketone).

5α-*Fluorocholestane*-3 : 6-*dione* (XI).—A solution of 3β-acetoxy-5α-fluorocholestan-6β-ol (0·33 g.) and lithium aluminium hydride (96 mg.) in dry ether (20 c.c.) was heated under reflux. Isolation with ether yielded 5α-fluorocholestane-3β : 6β-diol (0·28 g.), m. p. 196—197° (from ethyl acetate), $[\alpha]_D$ +13°. [Acetylation of the diol gave 3β : 6β-diacetoxy-5α-fluorocholestane, m. p. and mixed m. p. 124—125° and 160—161°.] The diol (0·22 g.) in acetone (8 c.c.) was treated dropwise with 8N-chromic acid until a yellow colour persisted. Isolation with ether and crystallisation from methanol afforded 5α-*fluorocholestane*-3 : 6-*dione* (0·14 g.), m. p. 143—144°, $[\alpha]_D$ +10° (Found: C, 77·9; H, 10·5. $C_{27}H_{43}O_2F$ requires C, 77·5; H, 10·3%). The compound showed no appreciable absorption in the ultraviolet region and gave a carbonyl band (1720 cm.$^{-1}$) but no hydroxyl band in the infrared spectrum.

A solution of the fluoro-diketone (36 mg.) in benzene was adsorbed on to alumina (5 g.). After 12 hr. the steroid was eluted with ether (30 c.c.). Crystallisation from methanol gave cholest-4-ene-3 : 6-dione, m. p. and mixed m. p. 124—126°.

3β-*Chloro*-6β-*fluorocholestan*-5α-*ol*.—Boron trifluoride–ether complex (0·5 c.c.) was added to a solution of 3β-chloro-5α : 6α-epoxycholestane (0·6 g.) in benzene (20 c.c.) at 20°. After 18 min. the product was isolated with ether: it showed negligible carbonyl absorption near 1700 cm.$^{-1}$. Two crystallisations from methanol–acetone afforded 3β-*chloro*-6β-*fluorocholestan*-5α-*ol* (278 mg.), m. p. 129—131°, $[\alpha]_D$ 0° (Found: C, 73·85; H, 10·7; Cl, 8·1. $C_{27}H_{46}OClF$ requires C, 73·55; H, 10·45; Cl, 8·05%): infrared spectrum (in CS_2), hydroxyl peak at 3580 cm.$^{-1}$.

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961. *Chemical Studies in the Biosynthesis of Purine Nucleotides. Part II.* The Synthesis of* N*-Glycyl-*D*-ribofuranosylamines.*

By J. Baddiley, J. G. Buchanan, R. Hodges, and J. F. Prescott.

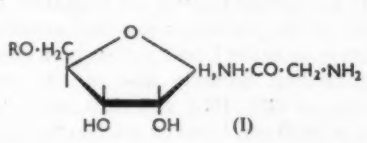
N-Glycyl-α- and -β-D-ribofuranosylamine (XII and its anomer) were synthesised in connection with studies on the synthesis of the natural purine nucleotide precursor " glycineamide ribotide " (I; R = PO_3H_2).

2 : 3 : 5-Tri-*O*-benzoyl-β-D-ribofuranosyl chloride (III) was converted into the β-azide (IV), then reduced to an unstable mixture of α- and β-forms of 2 : 3 : 5-tri-*O*-benzoyl-D-ribofuranosylamine (VIII). This reacted with benzyloxycarbonylglycyl chloride or with benzyloxycarbonylglycyl ethyl carbonate, and benzoyl groups were removed from the product. From the resulting mixture pure α- and β-forms of *N*-benzyloxycarbonylglycyl-D-ribofuranosylamine were separated by crystallisation. Hydrogenation yielded the *N*-glycyl compounds (XII and its anomer), conveniently isolated as their oxalates. The structure of these and intermediate products was confirmed by oxidation with periodate.

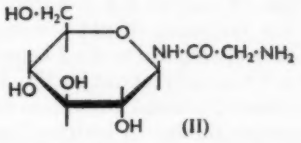
A method for the detection of *O*-acylated carbohydrate derivatives on paper chromatograms is described.

N-Glycyl-D-ribofuranosylamine 5-phosphate (" glycineamide ribotide ") (I; R = PO_3H_2) is believed to be an intermediate in the early stages of purine nucleotide biosynthesis. A compound with this structure has been isolated from natural sources [1,2,3] and shown to accumulate in systems where purine nucleotide synthesis has been inhibited at later stages. Although the purine nucleotides are β-glycosides, the configuration of the glycosyl residue in the precursor (I; R = PO_3H_2) has not been established. The synthesis of α- and β-forms of the riboside (I; R = H) and the corresponding phosphate (I; R = PO_3H_2) was of interest in connection with enzyme studies on the biosynthetic processes. Only one form of the phosphate is known to occur naturally, but when acidic conditions are used in its isolation two separable isomers are formed.[1] In suitable circumstances, both isomers are nucleotide precursors and it was thought that synthetic compounds with known configuration would assist in studies on the mechanism of their enzymic utilisation.

In Part I the synthesis of the model compound *N*-glycyl-β-D-glucopyranosylamine (II) was described.[4] The methods developed earlier have now been applied to the synthesis of ribofuranosyl derivatives. A preliminary account of this work has been published.[5]



(I)



(II)

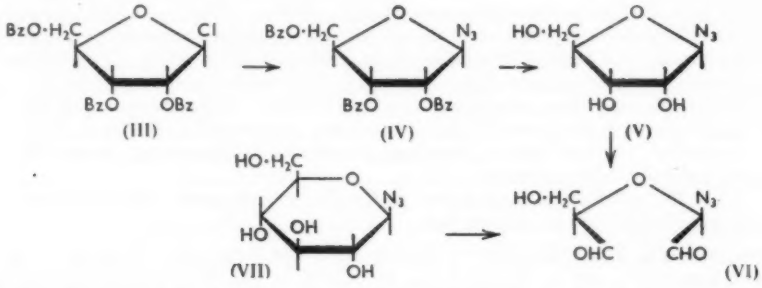
A convenient synthesis of the glucosylamine (II) involved reaction between 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosylamine and a suitable derivative of glycine. For a similar synthesis of the ribofuranosyl analogue (I; R = H) the hitherto unknown acyl derivatives of β-D-ribofuranosylamine would be required.

2 : 3 : 5-Tri-*O*-benzoyl-β-D-ribofuranosyl chloride [6] (III) was converted in high yield into the azide (IV) by reaction with sodium azide in methyl cyanide. The azide probably

* Part I, *J.*, 1956, 2818.

[1] Goldthwait, Peabody, and Greenberg, *J. Biol. Chem.*, 1956, **221**, 555.
[2] Peabody, Goldthwait, and Greenberg, *ibid.*, p. 1071.
[3] Hartman, Levenberg, and (J. M.) Buchanan, *ibid.*, p. 1057.
[4] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.
[5] Baddiley, Buchanan, Hodges, and Prescott, *Proc. Chem. Soc.*, 1957, 148.
[6] Kissman, Pidacks, and Baker, *J. Amer. Chem. Soc.*, 1955, **77**, 18.

possesses the β-configuration, since acylribofuranosyl halides normally give β-glycosides. A proof of the β-configuration of this compound was obtained by debenzoylation with sodium methoxide in methanol to β-D-ribofuranosyl azide (V), which was oxidised with sodium periodate to the dialdehyde (VI). Although this product was not isolated it had $[\alpha]_D^{20}$ −216°, in close agreement with the values found for this compound prepared in a similar manner from β-D-glucopyranosyl azide (VII). The structure of the glucopyranosyl azide is undisputed, both α- and β-forms being known.[7,8] The pronounced negative rotations of the azide (V) and its tribenzoyl derivative (IV) are also consistent with the β-D-ribofuranosyl structures.



Catalytic hydrogenation of 2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (IV) yielded the amino-sugar (VIII), characterised as a crystalline hydrochloride. The specific rotation of the hydrochloride in ethanol (+51·7°) did not alter significantly at room temperature during 24 hours. Experiments discussed below suggest that the β-compound mutarotates very readily and we consider that the positive specific rotation observed supports the view that the hydrochloride, even when freshly prepared, is an equilibrium mixture of α- and β-forms. In this respect it differs from the corresponding compound in the glucose series, 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosylamine, which, although it mutarotates under certain conditions,[9] is moderately stable. The relative instability of the ribose derivative is probably associated with the presence in it of a furanose ring. Attempts to crystallise the amino-sugar (VIII) were unsuccessful and resulted in the formation of a substance which was no longer basic. Analysis indicated that this was isomeric with the amino-sugar and was probably represented by (IX). In the α-form of the amino-sugar (VIII) the benzoyl residue at position 2 is in a sterically favourable position for migration to the amino-group. The migration should be complete as the β-amino-compound assumes the α-structure. The ready migration of a 2-benzoyl residue to the 1-position has been observed with 2 : 3 : 5-tri-*O*-benzoylribofuranose.[10] A potassium bromide disc of the neutral compound (IX) showed infrared absorption maxima at 3328, 1652, and 1526 cm.$^{-1}$, characteristic of a secondary amide. A hydroxyl band at 3425 cm.$^{-1}$ and an ester-carbonyl band at 1723 cm.$^{-1}$ were also present. In the hydrochloride of (VIII) the hydroxyl and amide absorptions were absent and there was an appropriate increase in the band at 1723 cm.$^{-1}$ together with a complex series of bands from 3300 to 2400 cm.$^{-1}$, characteristic of the $^+NH_3$ group.[11]

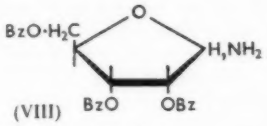
Freshly prepared 2 : 3 : 5-tri-*O*-benzoyl-D-ribofuranosylamine (VIII) reacted readily with benzyloxycarbonylglycyl chloride or benzyloxycarbonylglycyl ethyl carbonate, giving the glycine derivative (X) in 67% yield. In neither case did the product crystallise even after chromatography, but analysis indicated that it was reasonably pure. The gum had

[7] Bertho and Aures, *Annalen*, 1955, **592**, 54.
[8] Bertho, *Ber.*, 1930, **63**, 836.
[9] Bertho and Maier, *Annalen*, 1932, **498**, 50.
[10] Ness and Fletcher, *J. Amer. Chem. Soc.*, 1956, **78**, 4710.
[11] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954.

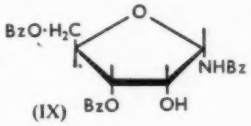
a low positive specific rotation, which suggested that it was a mixture of anomers. Removal of benzoyl groups from this with ammonia in methanol proceeded slowly, but sodium methoxide in methanol effected rapid debenzoylation. Crystallisation of the mixture from methanol gave the pure *N*-(benzyloxycarbonylglycyl)-α-D-ribofuranosylamine (XI), and the β-anomer was obtained from the mother-liquors as a monohydrate by crystallisation from water. The combined yield was excellent.

The structures of the benzyloxycarbonyl compounds (XI and its anomer) follow from their specific rotations (+76·6° and −34·4° respectively) and from their behaviour towards periodate. They each consumed one mol. of periodate without the formation of formic acid, and consequently must be furanosides. The specific rotation of the dialdehyde obtained from the isomer with $[\alpha]_D$ −34·4° agreed very closely with that derived from *N*-(benzyloxycarbonylglycyl)-β-D-glucopyranosylamine, whose configuration is firmly established.[4] It was necessary to carry out the periodate oxidations under slightly acidic conditions. This was particularly important with the ribofuranosyl derivatives where no formic acid is produced and consequently acidity does not develop. Under neutral conditions the dialdehydes formed were unstable and the optical activity of the products slowly disappeared.

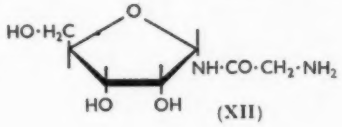
It should be noted that whereas the ribofuranosylamine (VIII) mutarotates with great ease its glycyl derivatives (XI and the β-anomer) are stable, at least under moderate conditions of pH and temperature. A similar greatly increased stability of glycyl derivatives was observed in the glucose series.[4] The stability of the furanose ring in the *N*-glycyl-



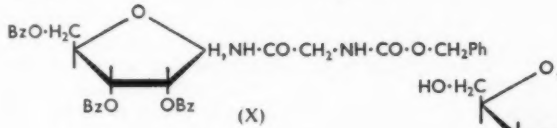
(VIII)



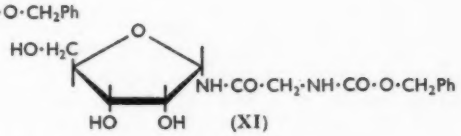
(IX)



(XII)



(X)



(XI)

ribofuranosylamines is noteworthy and recalls the behaviour of *N*-acetyl-D-glucofuranosylamine.[12] We conclude that the anomerisation which had occurred in the above synthesis of the *N*-(benzyloxycarbonylglycyl) compounds (XI and its anomer) took place immediately after hydrogenolysis of the azide to the amine (VIII), and not at a later stage. Even when the azide was hydrogenated in the presence of acetic anhydride a mixture of anomeric *N*-acetylribofuranosylamines was formed.

Hydrogenolysis of the benzyloxycarbonyl derivatives (XI and its anomer) gave the corresponding *N*-glycyl-α- and -β-D-ribofuranosylamines (XII and its anomer). Each compound was isolated as its hydrogen oxalate by adsorption on Amberlite IRC-50 resin and elution with oxalic acid solution. The hydrogen oxalate of the α-compound (XII) was crystalline. Each consumed one mol. of periodate and the dialdehyde from the β-compound had the same specific rotation as that obtained by similar oxidation of *N*-glycyl-β-D-glucopyranosylamine.[4]

The relation of the glycylribofuranosylamines (XII and its anomer) to natural nucleotide precursors must await further experiment. This may be achieved either by enzymic dephosphorylation of " glycineamide ribotide " or by chemical phosphorylation of the two synthetic ribosides at position 5.

[12] Hockett and Chandler, *J. Amer. Chem. Soc.*, 1944, **66**, 957.

Extensive use has been made during this work of paper chromatography. Glycosylamines and their *N*-substituted derivatives on paper chromatograms were readily detected by the periodate–Schiff method. As this method depends on the presence in the molecule of a 1 : 2-glycol system it could not be applied directly to the acetylated and benzoylated derivatives. Acetylated sugars have been detected on paper by spraying with hydroxylamine solution, followed by ferric chloride.[13] This method, which depends upon the formation of acylhydroxamic acids, is unsatisfactory with benzoylated sugars. We have found that both acetylated and benzoylated sugar derivatives can be readily detected by exposing the paper to the vapour from saturated methanolic ammonia in a chromatography tank for 12 hours, followed by spraying with the periodate–Schiff reagents.

This chromatographic method enabled the course of debenzoylation of tri-*O*-benzoylribofuranosyl derivatives with ammonia to be studied. It was found that benzoyl groups at positions 2 and 3 were removed much more readily than that at position 5. Conditions were found where debenzoylation at positions 2 and 3 was complete but little attack at the 5-position had occurred. Thus, a compound believed to be 5-*O*-benzoyl-β-D-ribofuranosyl azide was detected as a major product of the action of ammonia on 2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl azide. Also, the main product from 2 : 3 : 5-tri-*O*-benzoyl-*N*-(benzyloxycarbonylglycyl)-D-ribofuranosylamine (X) was probably the 5-*O*-benzoyl derivative.

Experimental

2 : 3 : 5-*Tri*-O-*benzoyl*-β-D-*ribofuranosyl Azide*.—1-*O*-Acetyl-2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranose (5·12 g., 1 mol.) was suspended in ether, saturated with hydrogen chloride at 0°, and kept at −14° for 10 days. Ether and hydrogen chloride were removed under reduced pressure at <5°. The residual gum was treated twice with benzene and once with toluene, followed by evaporation. There was finally no odour of acetic acid. The clear gum was dissolved in methyl cyanide (150 c.c.), finely ground sodium azide (5·1 g.; 7·7 mol.) was added, and the mixture stirred under reflux for 90 min. The solid was removed and washed with hot methyl cyanide. The combined filtrate and washings were evaporated to a gum, which was thrice dissolved in methanol and recovered by evaporation. Crystallised from methanol the *azide* (4·65 g., 94%) had m. p. 62—63°. Recrystallised from methanol, it had m. p. 66·5—67°, $[\alpha]_D^{22}$ −41·2° (*c* 2·97 in $CHCl_3$) (Found: C, 63·6; H, 4·7; N, 8·8. $C_{26}H_{21}O_7N_3$ requires C, 64·0; H, 4·3; N, 8·6%). The compound exists in two crystalline forms: large prisms, m. p. 62—63°, and fine needles, m. p. 66·5—67°. A mixture of the two forms has m. p. 63—64°.

β-D-*Ribofuranosyl Azide*.—The tribenzoate (1·0 g., 1 mol.) was suspended in dry methanol (10 c.c.), a solution of sodium (0·01 g., 0·2 mol.) in dry methanol (5 c.c.) added, and the mixture left overnight at room temperature. Excess of alkali was removed with Amberlite IRC-50 (H^+ form; methanol-washed) resin, and the solution was evaporated to a gum. This was dissolved in water (10 c.c.), extracted twice with ether (5 c.c.) to remove methyl benzoate, and evaporated to constant weight (0·3 g., 83%), $[\alpha]_D^{20}$ −193° (*c* 1·77 in H_2O). The product did not crystallise but was chromatographically pure. The dialdehyde produced by periodate oxidation had $[\alpha]_D^{20}$ −216° (*c* 1·41 in H_2O). β-D-Glucopyranosyl azide, $[\alpha]_D^{21}$ −28·9° (*c* 1·28 in H_2O), gave a dialdehyde with $[\alpha]_D^{20}$ −212° (*c* 0·86 in H_2O).

2 : 3 : 5-*Tri*-O-*benzoyl*-β-D-*ribofuranosylamine Hydrochloride*.—The tri-*O*-benzoyl-β-D-ribofuranosyl azide (1·0 g.) was dissolved in ethyl acetate (25 c.c.), Adams catalyst (0·1 g.) added, and the mixture hydrogenated at room temperature and pressure for 90 min. There was no change in gas volume. Magnesium sulphate (anhydrous) was added and after 10 min. the solids were filtered off and washed with ethyl acetate. Ether (16 c.c.) saturated with hydrogen chloride was added to the filtrate and washings. The resulting colourless *hydrochloride* (0·78 g., 76%), m. p. 124—127° (decomp.), was filtered off and washed with ether. Recrystallised from ethanol–ether it (0·28 g.) had m. p. 142—143·5°, $[\alpha]_D^{20}$ +51·7° (*c* 0·92 in EtOH) (Found: C, 63·4; H, 5·2; N, 2·9. $C_{26}H_{24}O_7NCl$ requires C, 62·7; H, 4·9; N, 2·8%). The specific rotation did not change significantly during 24 hr. at room temperature.

3 : 5-*Di*-O-*benzoyl*-N-*benzoyl*-α-D-*ribofuranosylamine*.—Tri-*O*-benzoyl-β-D-ribofuranosyl azide (0·5 g.) was hydrogenated as before for 4¼ hr. After removal of catalyst the solvent was

[13] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

evaporated to a gum which slowly crystallised from dry methanol. The *product* (0·19 g., 40%) had m. p. 138—143°. Recrystallised from dry methanol it had m. p. 160—164°, $[\alpha]_D^{22}$ +60·8° (*c* 1·92 in $CHCl_3$) (Found: C, 67·7; H, 6·1; N, 3·1. $C_{26}H_{23}O_7N$ requires C, 67·7; H, 5·6; N, 3·1%).

2 : 3 : 5-*Tri*-O-*benzoyl*-N-(*benzyloxycarbonylglycyl*)-α,β-D-*ribofuranosylamine*.—Tri-*O*-benzoyl-β-D-ribofuranosyl azide was reduced in ethyl acetate (25 c.c. per g. of azide) with Adams catalyst (10%) at room temperature and pressure for 90 min., treated with anhydrous magnesium sulphate, and filtered. The resulting solution was used immediately.

(a) *Acid chloride method.* Benzyloxycarbonylglycyl chloride (from 3·07 g. of acid, 3 mol.) in chloroform (5 c.c.) was mixed at −5° with the amine solution (from 2·38 g. of azide, 1 mol.). After 5 min., pyridine (2·5 c.c., 6 mol.) was added, and the solution kept at −5° for 20 min. and at room temperature for 2 hr. The mixture was diluted with chloroform (180 c.c.) and washed with 2N-hydrochloric acid (twice), water, saturated sodium hydrogen carbonate solution, and water (150 c.c. of each). The chloroform layer was dried (Na_2SO_4) and evaporated to a gum. The gum was dissolved in benzene–light petroleum (b. p. 60—80°) (3 : 1) and chromatographed on neutral alumina (300 g.). After the column had been washed with benzene–chloroform mixtures the product was eluted with pure chloroform—in about 500 c.c. of solution. Evaporation left a gummy amide (2·13 g., 67% based on azide), $[\alpha]_D^{20}$ +6·2° (*c* 3·0 in $CHCl_3$) (Found: C, 65·3; H, 5·3; N, 4·4. Calc. for $C_{36}H_{32}O_{10}N_2$: C, 66·3; H, 4·9; N, 4·3%).

(b) *Carbonic anhydride method.* Ethyl chloroformate (2·33 c.c., 3 mol.) was added dropwise to a solution of benzyloxycarbonylglycine (5·16 g., 3 mol.) and triethylamine (3·22 c.c., 3 mol.) in dry ethyl acetate (75 c.c.) cooled to −20°. After 10 min. the amine solution [from azide (4·0 g., 1 mol.)] was added at −5° and the mixture kept at this temperature for 10 min., then allowed to warm to room temperature overnight. The solution was washed with 2N-hydrochloric acid (twice), water, saturated sodium hydrogen carbonate solution, and water. Evaporation of the dried ($MgSO_4$) solution to small volume gave crystals of benzyloxycarbonylglycine anhydride (1·74 g.), m. p. 117—121°, raised to m. p. 120·5—124° by recrystallisation from ethyl acetate. The mother-liquors were evaporated to dryness and chromatographed on neutral alumina as before, to give a gum (3·48 g., 68% based on azide), $[\alpha]_D^{21}$ +11·4° (in $CHCl_3$). Careful rechromatography on neutral alumina failed to yield crystalline material.

N-(*Benzyloxycarbonylglycyl*)-α- *and* -β-D-*ribofuranosylyamine*.—The foregoing tribenzoate (3·48 g., 1 mol.) was dissolved in a little dry methanol, and sodium methoxide (from 0·012 g. of sodium; 0·1 mol.) in methanol (5 c.c.) added at room temperature. After 12 hr. crystals of the α-form (0·65 g.), m. p. 163—164°, were filtered off. The filtrate was treated with Amberlite IRC-50 (H^+; methanol-washed) resin until neutral. The solution was evaporated to a gum which yielded the α-form (0·27 g.), m. p. 158—163°, on trituration with methanol. The filtrate was evaporated and the residue was dissolved in water, washed with ether (twice), evaporated to small volume, and inoculated with the β-form. A fraction (0·14 g.), m. p. 87—140° (containing α,β-forms), separated, followed by another (0·44 g.), m. p. 80—86° (mainly β-form). The total yield of crystals was 1·50 g. (83%).

The α-containing fractions were combined and recrystallised from methanol. The pure α-*compound* had m. p. 169—170·5°, $[\alpha]_D^{20}$ +76·6° (*c* 1·06 in H_2O), $[\alpha]_D^{18}$ +63·6° (*c* 0·98 in pyridine) (Found: C, 53·0; H, 5·4; N, 8·0. $C_{15}H_{20}O_7N_2$ requires C, 52·9; H, 5·9; N, 8·2%).

The pure β-*compound* crystallised from water, with m. p. 98—101°, $[\alpha]_D^{20}$ −34·4° (*c* 1·96 in H_2O), $[\alpha]_D^{20}$ −31·9° (*c* 0·88 in pyridine) (Found: C, 50·7; H, 6·3; N, 7·2. $C_{15}H_{20}O_7N_2.H_2O$ requires C, 50·4; H, 6·2; N, 7·5%). Seed crystals of the β-form were initially obtained from β-enriched mother-liquors by countercurrent distribution. In a butan-1-ol–water system, 50 transfers effected separation from a small amount of β-D-ribofuranosyl azide, $[\alpha]_D^{20}$ −193°, and the main peak yielded crystalline material.

Periodate Oxidations.—The α-compound consumed 0·97 mol. of sodium metaperiodate, giving a dialdehyde of $[\alpha]_D^{20}$ +35·7° (*c* 0·79 in H_2O). The β-compound consumed 1·00 mol., the dialdehyde having $[\alpha]_D^{20}$ −72·4° (*c* 0·94 in H_2O). *N*-Benzyloxycarbonylglycyl-β-D-glucopyranosylamine gave a dialdehyde with $[\alpha]_D^{20}$ −69·7° (*c* 1·69 in H_2O).

N-*Glycyl*-α-D-*ribofuranosylamine Hydrogen Oxalate*.—*N*-Benzyloxycarbonylglycyl-α-D-ribofuranosylamine (0·65 g., 1 mol.) was hydrogenolysed in 50% aqueous ethanol in the presence of palladium. The evolved carbon dioxide was absorbed by concentrated sodium hydroxide in a side-arm to the reaction vessel and hydrogenation was complete in 70 min. The solution was filtered from the catalyst, which was washed with aqueous ethanol. The combined filtrate

and washings were evaporated to about half-volume and adsorbed on a column of Amberlite IRC-50 resin (H^+ form; 1·5 × 12·0 cm.). The column was washed with water (100 c.c.) and the product was eluted with 0·1M-oxalic acid, 10 c.c. fractions being collected. A drop of each fraction was examined on paper by using the ninhydrin reaction. Fractions 2—7 were combined and evaporated to a semicrystalline residue. This was dissolved in water (10 c.c.) and ethanol was added gradually until there was no further precipitation. The *oxalate* (0·37 g.), m. p. 131—134° (decomp.), was collected. Recrystallisation from water–ethanol gave a product (0·30 g., 53%) with m. p. 148—151° (decomp. with evolution of gas), $[\alpha]_D^{23}$ +88·9° (*c* 0·73 in H_2O) (Found: C, 36·7; H, 5·4; N, 9·0. $C_9H_{16}O_9N_2$ requires C, 36·5; H, 5·4; N, 9·5%). On periodate oxidation, 0·96 mol. of oxidant was consumed. The resulting dialdehyde had $[\alpha]_D^{20}$ +36·4° (*c* 0·47 in H_2O).

N-Glycyl-β-D-ribofuranosylamine Hydrogen Oxalate.—This was prepared from the β-benzyloxycarbonyl compound (0·38 g.) in a manner similar to that described above for the α-compound. After adsorption and elution from an ion-exchange resin the ninhydrin-positive fractions were evaporated to a gum. This was reprecipitated from water (1 c.c.) by addition of ethanol (24 c.c.). Solvents were decanted and the residue of *oxalate* was evaporated to a foam (0·14 g., 48%), $[\alpha]_D^{18}$ −49·7° (*c* 1·13 in H_2O) (Found: C, 36·6; H, 6·8; N, 9·8%). On oxidation 0·98 mol. of sodium periodate was consumed and the resulting dialdehyde had $[\alpha]_D^{18}$ −92·7° (*c* 0·54 in H_2O). The dialdehyde obtained by oxidation of *N*-glycyl-β-D-glucopyranosylamine had $[\alpha]_D^{18}$ −91·9° (*c* 0·71 in H_2O).

Paper Chromatography.—The general methods were similar to those used in Part I. *O*-Acyl derivatives were detected in the following manner: The air-dried papers were hung in a chromatography tank above saturated methanolic ammonia for 12 hr. at room temperature. Excess of ammonia was allowed to diffuse from the papers during 2 hr. and the paper was sprayed with the periodate–Schiff reagents.

R_F Values.

Compound	Ninhydrin	IO_4^-/ Schiff	BuOH–AcOH	PrOH–NH_3
Tri-*O*-benzoyl-β-D-ribofuranosyl azide	—	+ *	0·98	
5-*O*-Benzoyl-β-D-ribofuranosyl azide	—	+	0·91	
β-D-Ribofuranosyl azide	—	+	0·63	
Tri-*O*-benzoyl-*N*-(benzyloxycarbonylglycyl)-D-ribofuranosylamine	—	+ *	0·97	
5-*O*-Benzoyl-*N*-(benzyloxycarbonylglycyl)-D-ribofuranosylamine	—	+	0·91	
N-(Benzyloxycarbonylglycyl)-α- and -β-D-ribofuranosylamines	—	+	0·67	0·89
N-Glycyl-α- and -β-D-ribofuranosylamines	+ (Yellow)	+	0·16	0·66
Glycine	+ (Purple)	—	0·18	0·51
Ribose	—	+	0·28	0·62

* After ammonia treatment.

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962. *The Preparation and Properties of Stannic Alkoxides.*

By D. C. Bradley, E. V. Caldwell, and W. Wardlaw.

Reactions involving alcoholic solutions of stannic chloride with either sodium alkoxides or ammonia were investigated and for different reasons found unsuitable for preparing stannic alkoxides. The last were obtained by alcohol interchange involving the *iso*propoxide *iso*propyl alcoholate $Sn_2(OPr^i)_8,2Pr^iOH$ which was itself obtained by a four-stage process involving the double alkoxide $Na\,Sn_2(OEt)_9$ and the *tert.*-amyloxide as intermediates. The properties of stannic alkoxides are compared with those of the corresponding titanium and zirconium compounds.

Little is known about stannic alkoxides. Meerwein and Bersin [1] claimed to have isolated the tetraethoxide from the reaction of stannic chloride with the requisite quantity of sodium ethoxide although they mentioned that a double alkoxide $Na\,H_3[Sn(OEt)_6]_2$ was sometimes obtained. Thiessen and Koerner [2] reported that the same reaction gave the alkoxy-acid $H_2[Sn(OEt)_6]$. In reinvestigating this system we obtained none of these compounds, but obtained quantitatively the double alkoxide $NaSn_2(OEt)_9$ by reaction (1). The analogous *iso*propoxide was also obtained. In view of the successful preparation of alkoxides of titanium, germanium, zirconium, and hafnium through the tetrachloride, alcohol, and ammonia we tried this method with stannic chloride. Using either ethyl or *iso*propyl alcohol, we obtained substances containing appreciable amounts of chloride and ammonia (or amido-groups), and the method did not yield pure stannic alkoxides. The affinity of nitrogen for co-ordination with tin was further emphasised by the preferential formation of the complex $SnCl_4,2C_5H_5N$ in the reaction of stannic chloride, pyridine, *tert.*-amyl alcohol, and ammonia in an attempt to prepare tin *tert.*-amyloxide. Stannic alkoxides were eventually obtained pure by the following route:

$$2SnCl_4 + 9NaOEt = NaSn_2(OEt)_9 + 8NaCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Na\,Sn_2(OEt)_9 + HCl = 2Sn(OEt)_4 + NaCl + EtOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$Sn(OEt)_4 + 4CMe_2Et{\cdot}OH = Sn(O{\cdot}CMe_2Et)_4 + 4EtOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$Sn(O{\cdot}CMe_2Et)_4 + 5Pr^iOH = Sn(OPr^i)_4,Pr^iOH + 4CMe_2Et{\cdot}OH \quad . \quad . \quad . \quad . \quad (4)$$

$$Sn(OPr^i)_4,Pr^iOH + 4ROH = Sn(OR)_4 + 5Pr^iOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The stannic ethoxide produced by reaction (2) is impure owing to some hydrolysis and the presence of sodium chloride. As the stannic *iso*propoxide obtained in an analogous reaction was more hydrolysed the hydrolysis is probably caused by water produced in a side reaction involving alcohol and hydrochloric acid. In an attempt to avoid hydrolysis a reaction was tried with tin trichloride monoethoxide ethanolate in place of hydrochloric acid:

$$SnCl_3(OEt),EtOH + 3Na\,Sn_2(OEt)_9 = 7Sn(OEt)_4 + 3NaCl + EtOH$$

However, the stannic ethoxide was still contaminated with sodium chloride. These difficulties were overcome by subjecting the impure stannic ethoxide to reaction (3) and distilling out the volatile tin tetra-*tert.*-amyloxide. Reaction (4) was facilitated by the small solubility of stannic *iso*propoxide *iso*propyl alcoholate in *iso*propyl alcohol from which it is readily crystallised; the crystalline *iso*propyl alcoholate was an excellent starting material for the preparation of several stannic alkoxides [reaction (5), R = Me, Et, Pr^n, Bu^s, Bu^t, *n*-C_5H_{11}, *tert.*-C_5H_{11}, and $EtMe_2C$]. None of the primary alkoxides could be volatilised even under very low pressure without decomposition and in this respect they differ remarkably from the primary alkoxides of titanium, germanium, and zirconium. On the

[1] Meerwein and Bersin, *Annalen*, 1929, **476**, 113.
[2] Thiessen and Koerner, *Z. anorg. Chem.*, 1931, **195**, 88.

other hand there is a striking similarity in the volatilities of the *monomeric* tertiary alkoxides as shown in Table 1.

TABLE 1. *Boiling points of tertiary alkoxides.*

R in $M(OR)_4$	Ti	Sn	Zr
Me_3C	91°/4·2 mm.	99°/4·0 mm.	85·5/4·0 mm.
Me_2EtC	98/0·1	102/0·2	95/0·1
$MeEt_2C$	128/0·1	140/0·4	128/0·1

The stannic *iso*propoxide *iso*propyl alcoholate was dimeric in boiling benzene and thus resembles in structure as well as crystalline form the corresponding derivatives of zirconium and cerium. Moreover, there is a further resemblance because a series of sodium zirconium alkoxides, with the formula $Na\ Zr_2(OR)_9$ analogous to the sodium tin alkoxides, have been prepared.[3] The lower thermal stability of tin alkoxides than of zirconium alkoxides applies also to the sodium double alkoxides. Thus although the sodium zirconium alkoxides could be volatilised unchanged under reduced pressure the tin compounds decomposed under similar conditions.

A similar reaction to that of stannic chloride, alcohol, and ammonia, giving stannic chloride alkoxide ammoniates (or amides), occurred when stannic chloride was replaced by the iodide. Further information was obtained by treating stannic *iso*propoxide with ammonium chloride in boiling benzene; a chloride *iso*propoxide ammoniate was produced suggesting that the final stage of dechlorination (eqn. 6) is reversible:

$$SnCl(OR)_3 + NH_3 + ROH \longrightarrow Sn(OR)_4 + NH_4^+ + Cl^- \quad . \ . \ . \ . \ . \ . \quad (6)$$

This equation also explains why the product of the ammonia reaction has a lower chloride content when alcohol–benzene rather than alcohol alone is used, because ammonium chloride is less soluble, so promoting the forward reaction. The stannic *iso*propoxide also reacted with liquid ammonia giving an ammoniate or amido-compound and this explains the presence of ammonia in the above products, *viz.*:

$$NH_3 + Sn(OR)_4 \longrightarrow Sn(OR)_4,NH_3 \text{ or } SnNH_2(OR)_3,ROH$$

EXPERIMENTAL

General experimental details were similar to those described previously.[4,5] Stannic chloride was refluxed for several hours with a little thionyl chloride and then fractionally distilled.

Analysis.—Compounds containing tin and chlorine but no sodium were analysed as previously described.[5] As this method was unsuitable for sodium, owing to the presence of a large amount of ammonium salts, the tin was precipitated with "Cupferron." Then the filtrate was evaporated to dryness, the organic matter carefully burnt off, and the sodium determined as sulphate. Ammonia was determined volumetrically in the distillate after a sample was distilled with sodium hydroxide in a Kjeldahl apparatus.

Reactions involving Stannic Chloride and Sodium Ethoxide.—(*a*) To tin trichloride monoethoxide ethanolate (3·62 g., 1 mol.) in ethyl alcohol (50 c.c.) was added sodium ethoxide (from 0·78 g. of Na, 3 mol.) in alcohol (20 c.c.) and the system was boiled for 3 hr. The sodium chloride was filtered off, and the filtrate evaporated to dryness to give the *double ethoxide* as a white solid [Found: Sn, 35·7; $Na\ Sn_2(OEt)_9$ requires Sn, 35·7%].

(*b*) The trichloride (47·3 g., 1 mol.) was caused to react with sodium ethoxide (from 12·14 g. of Na, 3·5 mol.) in boiling alcohol (100 c.c.). Removal of the sodium chloride by filtration followed by evaporation of the filtrate to dryness left a solid (38 g.) [Found: Sn, 35·6; EtO, 59·7; Na, 3·6. Calc. for $Na\ Sn_2(OEt)_9$: Sn, 35·7; EtO, 60·91; Na, 3·5%]. The double alkoxide was very soluble in benzene or carbon tetrachloride and less soluble in ether or light petroleum. It crystallised from alcohol. When heated in a short-path still under 0·1 mm. it did not sublime or melt below 260°, whereat it decomposed.

[3] Bartley and Wardlaw, to be published.
[4] Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 4204.
[5] Bradley, Caldwell, and Wardlaw, *J.*, 1957, 3039.

Attempts to prepare Stannic Ethoxide by the Sodium Method.—(a) *By the action of alcoholic hydrogen chloride on* $NaSn_2(OEt)_9$. The sodium tin ethoxide (10 g.) was caused to react with the requisite quantity of alcoholic hydrogen chloride (*ca.* 1% w/v) at the b. p. After filtering off the sodium chloride and evaporating the filtrate under reduced pressure we obtained the white solid *tetraethoxide* (7·1 g.) [Found: Sn, 38·7; EtO, 54·4. $Sn(OEt)_4$ requires Sn, 39·7; EtO, 60·3%].

(b) *By the reaction of* $SnCl_3(OEt),EtOH$ (1 *mol.*) *and* $NaSn_2(OEt)_9$ (3 *mol.*). The sodium tin ethoxide (6·1 g.) and tin trichloride monoethoxide ethanolate (0·98 g.) were caused to react in boiling alcohol (100 c.c.). The solid product (4 g.) (Found: Sn, 36·9; EtO, 54·2%), obtained after filtering off the precipitate and evaporating the filtrate to dryness, was contaminated with sodium chloride.

Stannic tert.-*Amyloxide.*—(a) *By the pyridine–ammonia method.* Stannic chloride (23 g.) reacted exothermically with *tert.*-amyl alcohol (44·2 g.), pyridine (38 g.), and benzene (115 g.). Treatment with ammonia caused no apparent change; the initially formed precipitate was stannic chloride dipyridinate (Found: Sn, 29·3; Cl, 33·2. Calc. for $SnCl_4,2C_5H_5N$: Sn, 28·3; Cl, 33·9%).

(b) *From tin chloride alkoxide ammoniates.* Stannic chloride (20 c.c.) was added slowly with stirring to ethyl alcohol (300 c.c.) and the solution then treated with excess of ammonia. After the ammonium chloride was filtered off the filtrate gave on evaporation a white solid (37 g.) (Found: Sn, 39·6; EtO, 50·8; Cl, 3·5; NH_3, 5·1%). This was caused to react with *tert.*-amyl alcohol (52 g.) in benzene (204 g.) and the ammoniacal ethyl alcohol–benzene azeotrope was removed by fractional distillation. Evaporation of solvent under reduced pressure left a dark brown viscous liquid (38·5 g.) which on distillation at 127°/0·1 mm. gave a yellow distillate (17 g.) [Found: Sn, 25·6; Cl, 0·3. Calc. for $Sn(OC_5H_{11})_4$: Sn, 25·4%]. The black non-volatile residue contained stannous tin. In a similar experiment with a tin chloride ethoxide ammoniate containing more chloride (38·2 g.; Sn, 38·7; EtO, 50·1; Cl, 6·4; NH_3, 5·8%) and *tert.*-amyl alcohol (48·5 g.) in benzene (500 c.c.), a viscous brown product (45 g.) was obtained but this decomposed when heated under reduced pressure and gave no tetra-*tert.*-amyloxide. Starting with a chloride-free tin ethoxide ammoniate (Sn, 38·3; EtO, 55·6%) we finally distilled out pure *stannic tetra*-tert.-*amyloxide* 106°/0·4 mm., and this was monomeric in boiling benzene [Found: Sn, 25·5%; *M*, 471·4. $Sn(OC_5H_{11})_4$ requires Sn, 25·4%; *M*, 467·3]. Similar results were obtained by starting from tin chloride *iso*propoxide ammoniates. For example, from the reaction involving the chloride *iso*propoxide ammoniate (29·1 g.; Sn, 31·5; Pr^iO, 62·7; Cl, 3·3; NH_3, 2·7%), and *tert.*-amyl alcohol (35·2 g.) in benzene (200 c.c.) a viscous residue was obtained which at 128°/0·8 mm. gave a yellow distillate (16·6 g.) (Found: Sn, 26·1; Cl, 0·7%) and a black residue (14 g.).

(c) *By the method involving sodium tin ethoxide.* This method gave the purest product. Sodium tin ethoxide (32·62 g.) was treated with the requisite boiling alcoholic hydrochloric acid (136 g.) for 2½ hr. The product (30·6 g.) obtained after filtering off sodium chloride and evaporating solvent from the filtrate still contained sodium chloride (Found: Sn, 37·9; EtO, 54·9; Cl, 4·1; Na, 2·5%). The impure ethoxide (28·1 g.) was then treated with *tert.*-amyl alcohol (50 g.) in benzene (200 c.c.). During this alcohol interchange more sodium chloride was deposited. After filtration and evaporation of the filtrate a viscous liquid (41·5 g.) was left. This was distilled at 100°/0·2 mm. and gave a colourless distillate (31·6 g.) (Found: Sn, 25·5%).

Stannic iso*Propoxide.*—Addition of *iso*propyl alcohol (100 c.c.) to stannic *tert.*-amyloxide (31·0 g.) caused immediate deposition of crystals which dissolved when refluxed for 2 hr. A crystalline mass appeared on cooling. Two further recrystallisations from *iso*propyl alcohol afforded the *stannic* iso*propoxide* iso*propyl alcoholate* (Found: Sn, 28·8; Pr^iO, 71·4%; *M*, 833·4. $Sn_2(OPr^i)_8.2Pr^iOH$ requires Sn, 28·6; Pr^iO, 71·2%; *M*, 830·4). The alcoholate (3 g.), heated at 90° under reduced pressure, lost *iso*propyl alcohol and the viscous residue was distilled at 131°/1·6 mm. giving a viscous distillate which set to a wax of *stannic tetra*iso*propoxide* (1·2 g.) [Found: Sn, 34·0; Pr^iO, 66·1; $Sn(OPr^i)_4$ requires Sn, 33·4; Pr^iO, 66·6%].

Stannic Alkoxides prepared from the iso*Propoxide.*—Several *stannic alkoxides* were obtained by alcohol interchange of the *iso*propoxide *iso*propyl alcoholate. The reactions were conducted in benzene and, except for the preparations of the methoxide and ethoxide, were facilitated by the azeotropic removal of the *iso*propyl alcohol by fractional distillation. In the cases involving alcohols less volatile than *iso*propyl, the fractional distillation was replaced by a rapid evaporation of the mixed alcohols under reduced pressure. This process was repeated with fresh

quantities of the less volatile alcohol until analysis of the product showed that interchange was complete. The results are shown in Table 2.

TABLE 2.

R in $Sn(OR)_4$	$Sn(OPr^i)_4$,Pr^iOH (g.)	C_6H_6 (g.)	ROH (g.)	$Sn(OR)_4$ (g.)	Sn (%) Found	Sn (%) Required
Pr^n	4·2	160	11·0	2·8 [a]	33·6	33·4
Bu^s	7·2	150	15·3	7 [b]	29·2	28·9
Bu^t	10·0	—	*c*	8·8 [d]	29·2	28·9
Me	4·0	80	30 + 30 + 30	2·9 [e]	48·0	48·8
Et	4·0	—	50 + 50 + 50	3·5 [f]	39·9	39·7
Me_2EtC	5·0	100	8·5	6·0 [g]	25·7	25·4
Et_2MeC	4·8	100	5·9	4·0 [h]	22·9	23·2

[a] Viscous liquid appearing to boil at 120°/0·03 mm. (decomp.). [b] Solid, m. p. *ca.* 100°/0·2 mm. and sublimed (decomp.) at 154°/0·2 mm. [c] Three successive amounts (500 c.c.) of benzene–*tert.*-butyl alcohol azeotrope used. [d] Solid, m. p. *ca.* 40°, distilled at 50°/0·1 mm. and at 99°/4·0 mm. (Found: Bu^tO, 70·3. Required: Bu^tO, 71·1%). [e] Solid, decomp. at 180°/0·1 mm. [f] Solid, decomp. at 175°/0·05 mm. (Found: EtO, 59·1. Required: EtO, 60·3%). [g] Viscous liquid appearing to boil at 160°/0·1 mm. (decomp.). [h] Liquid, distilled at 140°/0·4 mm.

Reaction between Stannic iso*Propoxide and Ammonium Chloride.*—Stannic *iso*propoxide (5 g.) was caused to react with ammonium chloride (2 g.) in boiling benzene (100 c.c.). After 20 min. ammonia was detected and after 6 hr. the system was cooled, unchanged ammonium chloride filtered off, and the filtrate evaporated to leave a solid (3 g.) (Found: Sn, 41·6; Cl, 10·1; NH_3, 3·9%. Cl/Sn, 0·69; NH_3/Sn, 0·82). A separate experiment confirmed that ammonium chloride was negligibly soluble in benzene and that the presence of chloride and ammonia in the product resulted from a reaction between the alkoxide and ammonium chloride.

Reaction between Stannic iso*Propoxide and Liquid Ammonia.*—Ammonia was condensed on stannic *iso*propoxide at *ca.* −80° and allowed to stand for 1 hr. Removal of ammonia under reduced pressure left a white solid (Found: Sn, 37·1; NH_3, 4·5%. NH_3/Sn, 0·89).

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963. *Chemical Properties of Tungsten Hexafluoride.*

By H. C. CLARK and H. J. EMELÉUS.

Pure tungsten hexafluoride does not react with alkali-metal fluorides under strictly anhydrous and grease-free conditions. With sulphur trioxide a fluorosulphate, $WF_2(SO_3F)_4$, is formed. New addition compounds of tungsten hexafluoride with ammonia, pyridine, and methylamine are described.

As molybdenum hexafluoride [1] and vanadium pentafluoride,[2] after careful purification, can be satisfactorily studied in grease- and moisture-free glass apparatus, we examined some reactions of tungsten hexafluoride under similar conditions. That association followed by self-ionisation is less likely in tungsten hexafluoride than in the liquid pentafluorides of the Group VA elements is suggested by the normal value of Trouton's constant [3] (21·5) as compared with the abnormally high values of 33·1 and 25·4 found for vanadium [2] and niobium pentafluorides [4] respectively.

Previous investigations of tungsten hexafluoride [5,6] have been largely qualitative and

[1] O'Donnell, *J.*, 1956, 4681.
[2] Clark and Emeléus, *J.*, 1957, 2119.
[3] Ruff and Ascher, *Z. anorg. Chem.*, 1931, **196**, 413.
[4] Fairbrother and Frith, *J.*, 1951, 3051.
[5] Ruff and Eisner, *Ber.*, 1905, **38**, 742.
[6] Priest and Schumb, *J. Amer. Chem. Soc.*, 1948, **70**, 2291.

many reaction products have not been identified. Cox, Sharp, and Sharpe [7] claimed that the hexafluoride is absorbed by alkali-metal fluorides to form the octafluorotungstates, M_2WF_8, but they were unable to use pure tungsten hexafluoride since their samples, prepared from bromine trifluoride and tungsten metal, were contaminated with bromine. Also their apparatus contained vacuum grease which may have reacted slowly with the hexafluoride. These reactions with alkali-metal fluorides have been re-examined and, contrary to the earlier results, tungsten hexafluoride was found not to combine with potassium or cæsium fluorides at room temperature, provided that all materials and apparatus were completely dry. Absorption of the hexafluoride was observed when insufficiently dried samples of potassium or cæsium fluorides or potassium hydrogen difluoride were used, but even in these cases it was not rapid. The products were probably mixtures of the alkali-metal oxyfluorotungstates and acid fluorides. Since the presence of bromine possibly caused the reactions previously reported, the action of tungsten hexafluoride with dry potassium and cæsium fluorides in the presence of free bromine was investigated; there was no reaction. It thus appears that pure tungsten hexafluoride does not react with the alkali-metal fluorides at room temperature, although the possibility of combination's occurring under different, as yet unknown, conditions is not eliminated.

Tungsten hexafluoride resembles niobium pentafluoride in virtually not reacting with sulphur dioxide at room temperature, although on long standing traces of thionyl fluoride and tungsten oxyfluoride are formed. With sulphur trioxide it forms the compound $WF_6,4{\cdot}5SO_3$, which can probably be formulated as the fluorosulphate $WF_2(SO_3F)_4$. Like the corresponding niobium and tantalum pentafluoride derivatives, $NbF_3(SO_3F)_2$ and $TaF_3(SO_3F)_2$, this is an involatile, viscous liquid which fumes in air and is vigorously hydrolysed by water. The discrepancy in the analytical figures is attributable to the difficulty of removing excess of sulphur trioxide. Four moles of sulphur trioxide react with each mole of hexafluoride, whereas with the niobium and tantalum compounds two moles of sulphur trioxide react per mole of pentafluoride. This may be related to the fact that tungsten hexafluoride can lose up to four fluorine atoms to form the oxyfluorides WOF_4 and WO_2F_2, while the Group VA pentafluorides form only one series, MOF_3. All the reactions of tungsten hexafluoride so far discussed show considerable differences from those of vanadium pentafluoride.[8]

The reaction of tungsten hexafluoride with anhydrous ammonia was studied by Ruff and Eisner,[5] who reported the formation of an orange-brown solid with gaseous ammonia and of a white solid with liquid ammonia; neither product was identified. The orange-brown solid has now been shown to be tetramminohexafluorotungsten(VI), $(NH_3)_4WF_6$. This was the only product with gaseous or liquid ammonia and the reported formation of a white solid was not confirmed. Tetramminohexafluorotungsten(VI) is hygroscopic, turns white in air, and dissolves in water to a purple solution which fairly rapidly becomes colourless in air. The compound thus seems similar to the ammonia derivative of tungsten oxytetrafluoride, $2WOF_4,NH_3$.[9]

With pyridine a similar type of addition compound, tripyridinehexafluorotungsten(VI), $(C_5H_5N)_3WF_6$, is formed. This is a white, hygroscopic solid which dissolves instantly in water with the formation of a similar transient purple colour. The origin of this colour is not clear, but titration of the purple solutions with oxidising agents showed that it was not due to lower valence states of tungsten. Attempts to convert tripyridinehexafluorotungsten(VI) into the pyridinium salt resulted in hydrolysis and the formation of oxyfluorotungstate and tungsten trioxide. This is to be expected in view of the doubtful existence of complex fluorides derived from tungsten hexafluoride.

Tungsten hexafluoride forms tri(methylamine)hexafluorotungsten(VI), $(CH_5N)_3WF_6$,

[7] Cox, Sharp, and Sharpe, *J.*, 1956, 1242.
[8] Clark and Emeléus, *J.*, 1957, 2119.
[9] Ruff, Eisner, and Heller, *Z. anorg. Chem.*, 1907, **52**, 256.

by reaction with dry methylamine. This is a white, hygroscopic solid, less stable than the pyridine derivative, and its aqueous solution also shows a transient purple colour.

Experimental

Tungsten hexafluoride was provided by the United Kingdom Atomic Energy Authority, whom we thank. Preliminary molecular-weight measurements showed it to be contaminated with hydrogen fluoride which was removed by passage through four tubes containing dry sodium fluoride. Its purity was determined by molecular-weight measurements in the apparatus described previously [1] and by analysis for tungsten by the cinchonine hydrochloride method and ignition to tungsten trioxide and, for fluorine, by precipitation as calcium fluoride (Found: W, 61·6; F, 38·3%; *M*, 298. Calc. for WF_6: W, 61·8; F, 38·2%; *M*, 298). The high-vacuum techniques previously described [1,2] were used throughout. Since tungsten hexafluoride is somewhat less reactive than vanadium pentafluoride, we could sometimes use systems in which metal Hoke valves replaced glass taps, or capillaries and break-seals. Care was taken to dry thoroughly all apparatus by flaming *in vacuo*.

Reaction of Tungsten Hexafluoride with Alkali-metal Fluorides.—Potassium fluoride (0·323 g.), dried *in vacuo*, was treated with excess of the hexafluoride at room temperature. After 15—30 min. the hexafluoride was pumped off. The residue weighed 0·312 g. In a similar experiment with excess of bromine the initial and final weights were 0·270 and 0·272 g. In neither case did the recovered fluoride contain tungsten. Damp potassium fluoride (0·201 g.) gave a residue weighing 0·277 g. after treatment with hexafluoride as above. A sample of undried potassium hydrogen difluoride (0·320 g.) increased in weight by 0·030 g. when similarly treated. Cæsium fluoride (0·283 g.), when treated as above with tungsten hexafluoride, gave a residue (0·282 g.) which was free from tungsten. A second sample (0·257 g.), which was not dry, increased in weight to 0·325 g. (Found: W, 15·3; F, 18·8. Calc. for Cs_2WF_8: W, 36·5; F 30·2%). In the reactions in which dry samples were used the glass was not etched. The purity of recovered hexafluoride was checked by molecular-weight measurements.

Reaction with Sulphur Dioxide.—Excess of dry sulphur dioxide was allowed to react with tungsten hexafluoride at room temperature for 24 hr. The volatile products were separated into fractions condensing at −78°, −112°, and −196°, leaving a small amount of an involatile, white solid. The −78° fraction was unchanged tungsten hexafluoride (Found: *M*, 296. Calc. for WF_6: *M*, 298), while the −112° fraction was sulphur dioxide (Found: *M*, 68·2. Calc. for SO_2: *M*, 64·0). The very small amount of material (0·015 g.) condensed at −196° was thionyl fluoride (Found: *M*, 86·1. Calc. for SOF_2: *M*, 86·0). The involatile white solid had a tungsten : fluorine ratio of 1 : 3·92 and was tungsten oxyfluoride, WOF_4.

Reaction with Sulphur Trioxide.—Tungsten hexafluoride and sulphur trioxide reacted slowly at room temperature forming, after several hours, a clear, viscous liquid. By heating the reaction trap to 50° *in vacuo* for several hours, all volatile substances were distilled off, but most of the product was involatile under these conditions. The small amount of volatile products was mainly excess of sulphur trioxide. The viscous liquid fumed in air and reacted vigorously with water, precipitating yellow tungsten trioxide. The *compound* gave analytical results corresponding to $WF_6,4{\cdot}5SO_3$ (Found: W, 28·0; SO_3, 54·7. $WF_6,4{\cdot}5SO_3$ requires W, 28·1; SO_3, 54·7%).

Reaction with Ammonia.—Gaseous ammonia was thoroughly dried over sodium and was then condensed in excess on tungsten hexafluoride. On warming to −64° a vigorous reaction occurred with the formation of an orange-brown solid. The mixture was kept for 2 hr. at −64°, after which the only remaining volatile material was excess of ammonia (Found: *M*, 17·1. Calc. for NH_3: *M*, 17·0). The orange-brown solid was *tetramminohexafluorotungsten*(VI) [Found: W, 49·0; F, 30·4; N, 15·2. $(NH_3)_4WF_6$ requires W, 50·3; F, 31·2; N, 15·3%].

Reaction with Pyridine.—Removal of excess of dry pyridine from its reaction mixture with tungsten hexafluoride, after reaction at room temperature for several hours, left an involatile, hygroscopic white solid which dissolved instantly in water giving a purple solution. This colour disappeared on standing. The white solid was *tripyridinehexafluorotungsten*(VI) [Found: W, 34·1; F, 21·8; C, 33·6; H, 2·6; N, 7·8. $(C_5H_5N)_3WF_6$ requires W, 34·4; F, 21·3; C, 33·7; H, 2·8; N, 7·9%]. Treatment of this compound with concentrated aqueous hydrofluoric acid gave a mixture of tungsten trioxide and oxyfluorotungstate.

Reaction with Methylamine.—Tungsten hexafluoride and dry methylamine reacted at −46° to give an involatile, white solid. The only volatile compound was excess of hexafluoride

(Found: *M*, 297). The white solid was extremely hygroscopic and produced a solution, initially purple but turning colourless on standing. Analysis showed the compound to be *tri(methylamine)hexafluorotungsten*(VI) [Found: W, 47·4; F, 28·7. $(CH_3NH_2)_3WF_6$ requires W, 47·1; F, 29·2%].

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964. *The Preparation and Properties of Some Plutonium Compounds. Part VI.* Plutonium Dioxide.*

By J. L. DRUMMOND and G. A. WELCH.

Several different forms of plutonium dioxide have been prepared. That made by ignition at 1200° is stoicheiometric; that prepared by direct ignition of metal at lower temperatures closely approaches stoicheiometric; and that prepared by ignition of plutonium salts at 870° in air has a higher molecular weight. We suggest that the dioxide has a formula in the range $PuO_{2\cdot00-2\cdot09}$ depending upon the starting material and ignition temperature.

SEABORG and WAHL,[1] and Harvey, Heal, Maddock, and Rowley,[2] reported that the only plutonium oxide stable to ignition in air was the dioxide. This observation was based on Zachariasen's *X*-ray diffraction evidence,[3] who found that the oxide had a fluorite-type face-centred cubic structure with a lattice parameter $a = 5{\cdot}386 \pm 0{\cdot}001$ *kX* units (equivalent to 5·396 Å) with four metal atoms per unit cell. The composition was confirmed by a microgravimetric examination of the reaction $Pu(IO_3)_4 \longrightarrow PuO_2$. Cunningham [4] reported that the stoicheiometry of the reaction $PuF_4 + 2H_2O \longrightarrow PuO_2 + 4HF$ verified the formula PuO_2. However, only minute quantities of plutonium were available for these early studies, and the weight changes involved would be insensitive to minor variations in the oxygen content of the oxide. Also the compositions of the iodate and fluoride were not known with certainty. Several authors [5-12] have reported the quantitative use of the dioxide ignited to 700—900° for plutonium determinations, including use in the measurement of specific activity.

Two other oxides of plutonium have been reported, a monoxide and a sesquioxide. No true oxide higher than PuO_2 is known; Westrum [5] reported that neither oxygen at 400°/70 atm., nor ozone at 800°, reacted with the dioxide.

We have now verified many of the early findings and provided new information about the preparation and properties.

The dioxide was produced by the ignition in air or oxygen of plutonium metal; of plutonium hydride, nitride, and carbide; of plutonium-(III) or -(IV) hydroxide, chloride, sulphate, nitrate, oxalate, fluoride, iodate, and peroxide; or of plutonium(VI) nitrate.

* Part V, *J.*, 1956, 3358.

[1] Seaborg and Wahl, *J. Amer. Chem. Soc.*, 1948, **70**, 1128.
[2] Harvey, Heal, Maddock, and Rowley, *J.*, 1947, 1010.
[3] Zachariasen, "The Transuranium Elements," McGraw-Hill Book Co. Inc., New York, 1949, p. 1442; *Acta Cryst.*, 1949, **2**, 388.
[4] Cunningham, "The Actinide Elements," McGraw-Hill Book Co. Inc., New York, 1954, p. 394.
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[10] Charman and Welch, C.I. Report 81 (U.K. Atomic Energy Authority).
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[12] Farwell, Roberts, and Wahl, *Phys. Rev.*, 1954, **94**, 363.

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The physical and chemical properties of the product depend upon the starting material and the temperature of ignition. The variation in appearance is shown in Table 1 for different samples of oxide.

TABLE 1. *Physical properties of plutonium dioxide ignited to* 870°.

Source	Colour	Appearance	Source	Colour	Appearance
Sulphate	Yellow-green to green	Bulky powder	Oxalate	Yellow-buff	Bulky powder
Nitrate	Dull yellow	Bulky solid	Iodate	Buff	Very bulky
Chloride	Dull yellow	Powder	Hydroxide	Black, traces of yellow	Dense shiny particles
Fluoride	Khaki, traces of black	Granules			

In general, the oxide was moderately reactive, and dissolved slowly in boiling mineral acids if it had not been heated above 500°. Highly ignited oxide was attacked only by fused sodium hydrogen sulphate or hot concentrated nitric acid containing a little hydrofluoric acid. The oxide prepared by igniting a plutonium salt at 870° reacted with hydrogen fluoride at 500° to form either the blue trifluoride or pink tetrafluoride, whereas that prepared directly from metal, and any plutonium oxide ignited to 1250°, were more resistant to attack.

Composition.—The variation in properties of different samples of dioxide caused doubt about the constancy of composition. Further, as a reproducible bias was found in the gravimetric assay of plutonium standard solutions by ignition of the sulphate at 700—1000°, the oxide appeared not to be stoicheiometric. The mean plutonium concentration for 15 determinations, the oxide being assumed to be $PuO_{2\cdot00}$, was 0·6% greater than the true value for the standard, which had been prepared from specially purified plutonium metal. The composition of the oxide was examined in order to understand this bias, which is equivalent to an oxide $PuO_{2\cdot10}$. It was not possible to determine the oxygen content directly, and the increase in weight during the conversion of metal into oxide was substituted. Pure, analysed samples of plutonium metal turnings which had been prepared and stored in an inert atmosphere were weighed, burnt in air, and ignited at 870°. The plutonium dioxide which was formed was ignited to constant weight; the average O/Pu atom ratio on 16 results was 2·010. The standard deviation was 0·4% of the ratio (0·05% of the oxide weight).

As this difference from stoicheiometry was insufficient to account for the observed bias in the assay of plutonium solutions, weighed samples of the same quality of plutonium metal were dissolved in sulphuric acid, and the plutonium sulphate was dried and ignited to oxide at 870°. The mean O/Pu atom ratio obtained was 2·07, in contrast to the value by direct ignition of metal. A third value for the ratio, 2·05, was obtained by the ignition of samples of plutonium nitrate, which had been prepared by dissolving plutonium metal in hydrochloric acid and converting the chloride into nitrate. The results are given in Table 2.

TABLE 2. *The* O/Pu *atom ratio of plutonium dioxide ignited to* 870°.

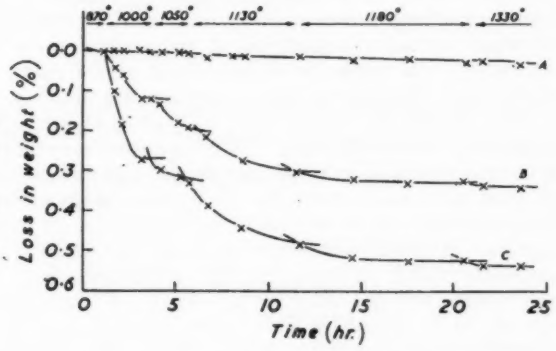
Material ignited	O/Pu atom ratio	
Plutonium metal	2·002, 2·005, 2·015, 1·999, 2·010, 2·018, 2·012, 2·024, 2·014, 2·011, 2·005, 1·995, 2·021, 2·015, 2·009, 2·002.	Mean = 2·010.
Plutonium sulphate	2·092, 2·059, 2·061, 2·063.	Mean = 2·07.
Plutonium nitrate	2·049, 2·028, 2·070.	Mean = 2·05.

The variation in the O/Pu atom ratio was proved by converting 2·01-oxide into an oxide with a higher ratio. Samples of oxide made directly from metal were weighed and repeatedly evaporated to dryness with sulphuric acid to form some plutonium sulphate, and were then reignited to oxide under the usual conditions. The O/Pu atom ratio always increased according to the percentage conversion into sulphate. The change was many times too great to be caused by impurity added with the sulphuric acid, or by conversion of impurities in the metal into stable sulphates.

As it seemed possible that the variation in the ratio was caused by incomplete

decomposition of plutonium sulphate or nitrate through ignition at too low a temperature, each of the three types of oxide was heated to higher temperatures, whereupon the samples lost weight each time the temperature was raised, more markedly if they were derived from plutonium salts, and they approached constant weight on continued heating at any given temperature. The heat-stability curves from 870° to 1330°, for oxide prepared from metal and from sulphate, and for a mixed sample, are reproduced in the Figure. A constant weight corresponding to the stoicheiometric dioxide was reached on ignition at 1180° and no further significant loss was observed on raising the temperature to 1330°. The O/Pu atom ratio at this temperature for the seven results in which the original weight of metal was known was always 2·002 ± 0·008.

The loss in weight on heating to between 870° and 1200° was not due to incomplete decomposition of the salt at the lower temperature, as constant weight was approached at each selected intermediate stage. Also, the necessary amount of oxides of nitrogen or



The heat stability of plutonium dioxide.
A, Plutonium dioxide made from metal.
B, Mixed plutonium dioxide sample.
C, Plutonium dioxide made from sulphate.

sulphur were not detected by mass spectrometry of the trace of gas evolved during the high-temperature ignition.

Shimomura, Tsubokawa, and Kojima [13] reported that nickel oxides of similarly high oxygen content can be prepared from nickel nitrate, the composition depending upon the ignition temperature, and approaching stoicheiometric on high-temperature ignition. We deduced that the weight loss which was observed when plutonium dioxide was heated to the stoicheiometric composition was the loss of the excess of oxygen from the system. The loss was measured accurately and gave $PuO_{2\cdot015}$, $PuO_{2\cdot046}$, and $PuO_{2\cdot089}$ as the most reliable formula for the oxides prepared at 870° from metal, nitrate, and sulphate respectively.

The *X*-ray diffraction powder photographs of the different types of oxide were examined for any change in lattice parameter or duplication of lines which might be caused by the variation in oxygen content. However, all samples produced photographs in agreement with the fluorite structure $a = 5\cdot396 \pm 0\cdot001$ Å obtained by Zachariasen, and no other phase was detected in any sample. In contrast, in the uranium–oxygen system at compositions close to UO_2, Alberman and Anderson [14] reported that a variable phase $UO_{2\cdot0}$—$UO_{2\cdot2}$ formed when the dioxide was gently heated in air or oxygen, but that this oxide disproportionated into two distinct cubic phases UO_2 and $UO_{2\cdot2}$ if it was annealed at higher temperatures. Hering and Perio,[15] Grønvold,[16] and Hoekstra and Siegel [17] also reported that annealed UO_2 has no appreciable range of composition.

[13] Shimomura, Tsubokawa, and Kojima, *J. Phys. Soc. Japan*, 1954, **9**, 521.
[14] Alberman and Anderson, *J.*, 1949, S303.
[15] Hering and Perio, *Bull. Soc. chim. France*, 1952, 351.
[16] Grønvold, *J. Inorganic Nuclear Chem.*, 1955, **1**, 357.
[17] Hoekstra and Siegel, "Proceedings of the International Conference on the Peaceful Uses of Atomic Energy," Vol. 7, United Nations, New York, 1956, p. 394.

The diffraction patterns of the oxides prepared from salts at 870° (especially from the nitrate) were less sharp than those from the high-temperature oxides, suggesting that the particle size of the oxides had increased on heating. Particle size may have influenced the physical and chemical properties of the oxides. The samples from plutonium salts ignited at 870° were bulky, hygroscopic, yellow or yellow-green powders which reacted very slowly with hot mineral acids, but the same samples ignited at 1200° all approached a darker, khaki colour, were much more compact, and showed neither affinity for water nor reactivity with acids except nitric acid containing a little hydrofluoric acid. But alternatively the variation in properties may have been due to a change in the oxide from a non-stoicheiometric form with many interstitial oxygen atoms or lattice defects to an ordered crystal structure.

Thorium oxide shows a similar variation of properties depending upon ignition conditions. It is widely reported that thoria requires ignition to more than 1100° to reach constant weight in accurate gravimetric analysis.[18] Like plutonium dioxide, thoria becomes non-hygroscopic and chemically inert at these temperatures. Thorium compounds are almost exclusively quadrivalent and no higher oxides are known, and there are no reports either to confirm or to dispute that a small range of variable composition may exist analogous to that suggested for plutonium dioxide.

For uranium the higher oxides U_3O_8 and UO_3 are well known, and in solution uranium is predominantly sexivalent. By comparison, no oxides of plutonium higher than PuO_2 have been reported, and the most stable valency in solution is Pu^{IV} although it is readily oxidised to the sexivalent state. In a review of the oxide systems of the actinide elements, Katz [19] related the formation of stable compounds over a range of composition to the existence of several oxidation states for the element and to their oxidation–reduction potentials. Such criteria indicate that plutonium dioxide may have a variable composition, and the range $PuO_{2\cdot0}$—$PuO_{2\cdot1}$ is compatible with the overall distribution of actinide oxides noted by Katz. The whole range of plutonium oxides, PuO—$PuO_{2\cdot1}$ is intermediate between the ranges reported for neptunium and americium.

Experimental

The toxicity of plutonium made it desirable to carry out all operations in a totally enclosed glove box, maintained at slightly reduced pressure and fitted with an air filter on the exhaust line. This was not possible however with the large high-temperature muffle furnace, which was placed in a well-draughted fume hood. Samples were first given a preliminary ignition to oxide inside a glove box. The balance was in a separate box and, although glove-box work was slower than normal, most operations were possible with only slight loss of facility.

The O/Pu *Atom Ratio of the* 870° *Oxides.*—Selected turnings of pure plutonium metal, freshly prepared in an inert atmosphere, were analysed for common metallic impurities and corrections were applied to all results in which the error was significant.

In the determination of the O/Pu ratio of oxide prepared by direct ignition, 0·2 g. samples of metal in silica weighing bottles were burned at a controlled rate in air by slowly raising the temperature. The oxide was then ignited to constant weight at 870°. The weight of oxide, which was not hygroscopic, was generally reproducible to within ±0·02% on a semimicro-balance.

When the oxide was prepared *via* plutonium sulphate, the weighed sample of metal was dissolved in dilute sulphuric acid. The solution was evaporated to dryness in a silica weighing bottle and the plutonium sulphate was decomposed to oxide by heating to 870° during 30 min. The oxide was ignited to constant weight at this temperature and was cooled in the closed weighing bottle in air dried by anhydrone [$Mg(ClO_4)_2$]. It was hygroscopic, and the weight was normally reproducible to ±0·05%.

When the oxide was prepared *via* the nitrate, the weighed metal was dissolved in dilute

[18] *E.g.*, Rodden and Warf, "Analytical Chemistry of the Manhattan Project," McGraw-Hill Book Co. Inc., New York, 1950, p. 160.
[19] Katz, *Record Chem. Prog.*, Spring 1951, **12**, 43–53.

hydrochloric acid. The solution was evaporated with an excess of nitric acid to form plutonium(IV) nitrate which was ignited to oxide as above.

The O/Pu Atom Ratio of the High-temperature Oxides.—0·2—0·5 g. samples of each of three types of plutonium oxide which had been ignited at 870° in platinum boats were further ignited to constant weight at successive temperatures in the range 1000—1330° in an electric muffle furnace. The samples were cooled over anhydrone and weighed rapidly to prevent adsorption of moisture. The oxides became less hygroscopic as the ignition temperature was raised; the weight of oxide was reproducible to within ±0·02% after ignition at 1200°.

X-Ray Crystallography.—All samples submitted for crystallographic examination were powdered and bound with Canada balsam, and were photographed in a 19 cm. powder camera with copper $K\alpha$ radiation.

Thanks are offered to Mr. B. J. McDonald for the crystallographic work, and acknowledgment is made to the Managing Director of the Industrial Group for permission to publish this paper.

UNITED KINGDOM ATOMIC ENERGY AUTHORITY (INDUSTRIAL GROUP),
WINDSCALE WORKS, CUMBERLAND. [*Received, April 15th*, 1957.]

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965. *The Preparation and Properties of Some Plutonium Compounds. Part VII.* Plutonium Carbides.*

By J. L. DRUMMOND, B. J. MCDONALD, HEATHER M. OCKENDEN, and G. A. WELCH.

Plutonium monocarbide, PuC, has been prepared by the reaction of graphite with plutonium metal or hydride at about 900°. A sesquicarbide, Pu_2C_3, was formed, in addition to the monocarbide, by the reduction of plutonium dioxide with graphite at 1800—1900°. Both carbides are reactive and easily hydrolysed by dilute acid or boiling water. Strong chemical and *X*-ray evidence suggests that a higher carbide exists but it has not been identified unequivocally.

CARBIDES of plutonium with the formulæ PuC and Pu_2C_3 have been reported, but there is very little information on their preparation and properties. They were identified by *X*-ray diffraction methods alone. Zachariasen [1] showed the presence of three distinct phases in the product from a micro-scale reduction of plutonium trifluoride with lithium in a graphite crucible. There were two face-centred cubic phases, corresponding to plutonium monoxide,[2] with the parameter $a = 4{\cdot}948 \pm 0{\cdot}002$ *kX* units (equivalent to 4·958 Å) which had been found in earlier work, and to plutonium monocarbide,[3] $a = 4{\cdot}910 \pm 0{\cdot}005$ *kX* units (4·920 Å). The third phase [1] was body-centred cubic, $a = 8{\cdot}11 \pm 0{\cdot}01$ *kX* units (later quoted as $8{\cdot}129 \pm 0{\cdot}001$ Å [4]), and was tentatively identified as the sesquicarbide by volume considerations. The composition was confirmed when the isostructural uranium sesquicarbide was prepared by Mallet, Gerds, and Vaughan.[5]

We have prepared these carbides by different methods and studied their chemical properties. As the carbon impurity in plutonium metal is likely to be present as carbide, these compounds may be of metallurgical significance.

Plutonium Monocarbide.—Preparation. Plutonium monocarbide was prepared by heating powdered graphite in an inert atmosphere with (*a*) plutonium hydride at 800° for 4 hr.,

* Part VI, preceding paper.

[1] Zachariasen, "The Transuranium Elements," McGraw-Hill Book Co. Inc., New York, 1949, Vol. II, p. 1449.
[2] Mooney and Zachariasen, *op. cit.*, p. 1442.
[3] Zachariasen, *Acta Cryst.*, 1949, **2**, 388.
[4] *Idem, ibid.*, 1952, **5**, 17.
[5] Mallet, Gerds, and Vaughan, *J. Electrochem. Soc.*, 1951, **98**, 505.

or (*b*) plutonium metal at 1000° for 5 hr., or (*c*) plutonium dioxide at 1800° for 10 min. In the last case sufficient graphite was used for the reaction $PuO_2 + 3C \longrightarrow PuC + 2CO$. The product was always a sintered, coke-like mass which could be broken into pale-grey crystalline fragments. The purest monocarbide was that prepared from plutonium hydride although, owing to the difficulty of mixing the reactants, the product contained small amounts of unchanged graphite and plutonium metal (which is formed on thermal decomposition of the hydride). Samples free from plutonium metal were prepared from intimate mixtures of the dioxide and graphite, but at the higher temperature required for this reaction some sesquicarbide was also formed. Where this contamination was found to be small by *X*-ray diffraction photography, the carbon content varied from 4·5 to 4·8% (PuC requires C, 4·78%).

Properties. Plutonium monocarbide began to oxidise slowly when heated to 200—300° in air, and it burned brightly in oxygen at 400°. In an inert atmosphere it melted at about 1850°. On cooling, the melt formed brittle pellets which sparked vigorously when broken, to expose shiny metallic surfaces. These surfaces remained bright even after two months in air at room temperature. Plutonium metal in the same circumstances would have been considerably oxidised. Samples prepared from hydride decomposed more rapidly in air, perhaps owing to their more porous nature.

The monocarbide was not attacked by cold water, but it effervesced steadily in hot water and precipitated plutonium(III) hydroxide. It was readily hydrolysed by cold dilute hydrochloric or sulphuric acid. The gas evolved in every case contained hydrogen and methane together with smaller quantities of ethane, butanes, acetylene, ethylene, and butenes, which were identified by mass spectrometry. There was only slight attack by nitric acid, but when the monocarbide was heated with concentrated nitric acid containing a little sodium fluoride there was a steady evolution of gas and carbon was deposited. A similar deposit of carbon was observed when uranium carbides were treated with nitric acid.

The *X*-ray diffraction patterns of eleven preparations of the monocarbide indicated a face-centred cubic system with a lattice parameter varying from 4·959 to 4·973 Å, as shown in the Table.

The lattice parameter of plutonium monocarbide.

Reactant	Temp.	Parameter (Å)	Reactant	Temp.	Parameter (Å)
Pu	1000°	4·969 ± 0·001	PuO_2	1650°	4·972 ± 0·001
$PuH_{2\cdot7}$	800	4·9695 ± 0·0005	PuO_2	1800	4·971 ± 0·003
$PuH_{2\cdot7}$	800	4·974 ± 0·0005	PuO_2	1800	4·972 ± 0·001
$PuH_{2\cdot7}$	800	4·959 ± 0·001	PuO_2	1800	4·973 ± 0·001
$PuH_{2\cdot7}$	1000	4·9705 ± 0·0005	PuO_2	1880	4·965 ± 0·002
$PuH_{2\cdot7}$	1650	4·969 ± 0·001			

The variation may be due to small amounts of plutonium monoxide or graphite existing in solid solution in the carbide, or possibly to a deficiency of carbon in the lattice. The fact that plutonium monocarbide and monoxide can exhibit mutual solubility was shown by heating a mixture of the two at 1650°. Although neither reactant was pure, their diffraction patterns were both visible in the mixture. In the sintered product they were replaced by one pattern with a parameter intermediate between the two. (The plutonium monoxide for this work was prepared by reducing the dioxide with plutonium hydride at 1800° in a tantalum crucible.) The corresponding uranium compounds have been more extensively studied and the lattice parameter of the isomorphous uranium monocarbide [6] is reported to vary from 4·948 to 4·995 Å. The monocarbide and monoxide form mutual solid solutions, but neither uranium nor carbon is appreciably soluble in the monocarbide.[7,8]

[6] Katz and Rabinowitch, "The Chemistry of Uranium," McGraw-Hill Book Co. Inc., New York, 1951, Vol. I, pp. 215, 249.
[7] Rundle, Baenzinger, Wilson, and McDonald, *J. Amer. Chem. Soc.*, 1948, **70**, 99.
[8] Mallet, Gerds, and Nelson, *J. Electrochem. Soc.*, 1952, **99**, 197.

The parameter $a = 4{\cdot}920$ Å reported by Zachariasen for plutonium monocarbide was obtained from a diffraction pattern in which three separate phases were identified and attributed to PuC, PuO, and Pu_2C_3 respectively. There was no reported chemical evidence for attributing the 4·92 phase to *pure* monocarbide, and it is likely that it had a different composition from the 4·97 phase found in this work. It is interesting to note that the plutonium monoxide mentioned above gave parameters $a = 4{\cdot}917$ and 4·938 for two preparations.

Plutonium Sesquicarbide.—Preparation. Plutonium sesquicarbide was prepared by heating an intimate mixture of plutonium dioxide and powdered graphite at 1850° for 10 min. The components were mixed in the ratio required to satisfy the equation $2PuO_2 + 7C \longrightarrow Pu_2C_3 + 4CO$. A slight excess of graphite or oxide was taken to allow for side reactions, depending upon whether a tantalum or a graphite crucible was used. The product melted at about 1900°; it closely resembled the monocarbide described above and often contained some of this compound or of a suspected higher carbide. The carbon content of the purer samples ranged from 6·2 to 7·1% (Pu_2C_3 requires C, 7·0%).

Properties. The chemical properties of the sesquicarbide differed from those of the monocarbide only in degree. Thus the former seemed slightly less stable to hydrolysis in the atmosphere, but more stable to oxidation on heating. The sesquicarbide was rather less easily hydrolysed by boiling water and by acids, the product containing solid or liquid hydrocarbons in the form of a wax in addition to a mixture of gaseous hydrocarbons similar to that from the monocarbide.

The *X*-ray diffraction powder photographs of the sesquicarbide gave a reproducible, body-centred cubic pattern with lattice spacing identical with those attributed to Pu_2C_3 by Zachariasen.[4]

Higher Carbides of Plutonium.—The existence of at least one higher carbide was strongly suspected although it was not possible to make a definite identification. Several preparations at temperatures above 2000°, made in graphite crucibles from mixtures rich in graphite, gave a new *X*-ray diffraction pattern whose stronger, distinguishing lines had "*d*" values of 3·31 (100), 3·08 (60), 1·56 (60), 1·52 (60), and 1·49 Å (60), the figures in parentheses being visual relative intensities. The full pattern does not include either of the carbide phases described above, and does not appear to resemble that of uranium dicarbide.[7,8] It has not yet been indexed.

The new *substance* melted at about 2200°, which is appreciably higher than the m. p. of plutonium sesquicarbide. It was much less stable in moist air than the known carbides, was more stable to oxidation, and formed a higher proportion of solid and liquid hydrocarbons on hydrolysis. The carbon content varied from 8·5 to 9·5% (PuC_2 requires C 9·1%). Some samples seemed to be less homogeneous than usual and gave poor duplicate analyses.

The temperature dependence of the formation of the higher carbide was demonstrated in two preparations in which a mixture of plutonium hydride and excess of graphite was used. In the first, at 1650°, the product contained a mixture of monocarbide and sesquicarbide, but in the second, at 2200°, the same reactants produced a mixture of the sesquicarbide and the higher carbide.

Comparison with Other Carbides.—The properties of all the plutonium carbides investigated are similar; chemically, they all belong to a class of reactive, heavy-metal carbides which includes UC_2, ThC_2, CeC_2, etc. For example, they are readily hydrolysed by dilute acid or hot water to form mixed hydrocarbons. Plutonium monocarbide, however, has the face-centred cubic structure and the metallic appearance of the interstitial monocarbides TiC, ZrC, HfC, and ThC, without their refractory nature and chemical inertness. Thence, although Wells [9] separates the thorium and uranium monocarbides into a separate class (interstitial) from their higher carbides (salt-like), this is not possible with plutonium carbides.

[9] Wells, "Structural Inorganic Chemistry," Oxford University Press, London, 1950, pp. 550, 704.

Plutonium monocarbide is much more reactive than uranium monocarbide, which is not attacked even by hydrochloric acid.[7] This difference also occurs between the mononitrides of plutonium and uranium.[10] Plutonium sesquicarbide also is more reactive than the uranium analogue which is not decomposed by water.[5]

Plutonium reacts with carbon at a lower temperature than does uranium and consequently the molten metal should not be handled in graphite containers.

Experimental

X-Ray Crystallography.—Specimens were bound with Canada balsam and photographed in a 19 cm. camera. Even semiquantitative interpretation was made difficult by the complex nature of the patterns, most of which contained several phases, some of them unidentified, and by the variation in particle size of the different phases. Further, the very hard products were often not homogeneous even when crushed. However, the general change in composition of the products with variation of reaction mixture was deduced from the *X*-ray analysis and the carbon content.

Carbon Determination.—To determine total carbon, 10 mg. samples were ignited at 900° in

Fig. 1. *High-temperature furnace.*

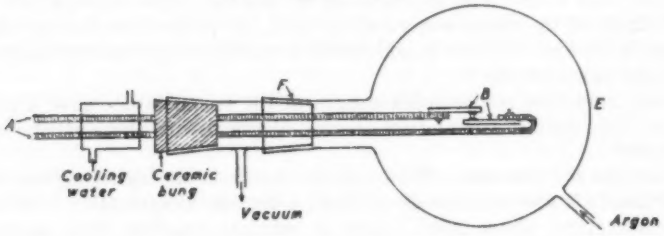

Fig. 2. *Electrode and crucible assembly.*

pure oxygen and the carbon dioxide formed was absorbed in 0·1N-barium hydroxide. The excess of alkali was back-titrated with standard acid. 95—100% recovery was obtained from 1 mg. standard graphite samples. In the free carbon determination, 20 mg. samples were hydrolysed with 2M-hydrochloric acid. The insoluble residue was centrifuged out, was washed successively with acid, water, acetone, and ether to remove solid or liquid hydrocarbons, and was then ignited as above.

The difference between the two results was the chemically combined carbon, which is the result reported here in all cases.

Preparations at 800—1000°.—The apparatus was that used previously for the preparation of plutonium hydride [11] and nitride [10] by Brown, Ockenden, and Welch. The sample of about 100 mg. of plutonium metal or plutonium hydride, mixed with pure powdered graphite in a small silica boat, was heated for several hours in a silica tube resistance furnace. The tube was continuously purged with dry argon, which was freed from oxygen and nitrogen by scrubbing with uranium turnings at 800°. Samples were cooled in the argon before removal.

Preparations at 1600—2200°.—A high-temperature microfurnace (Fig. 1), suitable for use in a glove box, was designed to heat a 100 mg. sample to 2200° for 10 min. periods. It operated on a variable A.C. supply of 0—6 v and 0—100 A. One-inch copper strip connectors *A* led into the glove box and were bolted to two small tantalum contacts *B*. A small tantalum or graphite crucible *C* and lid (Fig. 2) were sandwiched between thin graphite discs *D* and wedged between

[10] Brown, Ockenden, and Welch, *J.*, 1955, 4196.
[11] *Idem, ibid.*, p. 3932.

the tantalum contacts. Most of the heat was developed at the relatively high resistance of the crucible " sandwich," which was held in position by the resilience of the copper strip even at high temperatures. The furnace jacket *E* was a 1 l. Pyrex flask which was connected to the apparatus with a B.45 standard joint *F*. The apparatus was flushed with argon at 1—2 mm. pressure during operation of the furnace. After reaction the sample cooled to room temperature in a few minutes.

Crucible temperatures were measured with an optical pyrometer calibrated at 1770° by noting the apparent m. p. of platinum. Subsequent measurements were probably accurate to within 100°.

Thanks are offered to K. R. Melhuish for mass-spectrometric analyses of the hydrolysis gases; acknowledgment is made to the Managing Director of the Industrial Group of the U.K. Atomic Energy Authority for permission to publish this paper.

U.K. Atomic Energy Authority (Industrial Group),
Windscale Works, Cumberland. [*Received, April 15th,* 1957.]

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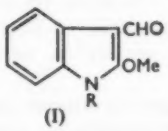
966. *Heterocyclic Compounds of Nitrogen. Part I. The Alkylation and Acylation of 3-Phenyloxindole, and the Preparation of Some Derivatives of 2-Hydroxy-3-phenylindole.*

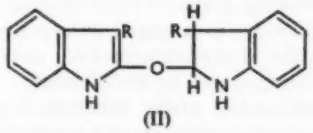
By J. Malcolm Bruce and F. K. Sutcliffe.

3-Phenyloxindole is alkylated at position 3, and acylated at position 1. 1-Substituted 3-phenyloxindoles are also alkylated at position 3, but acylation affords derivatives of 2-hydroxy-3-phenylindole, whose structures are established mainly by means of infrared and ultraviolet spectra.

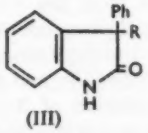
Several workers [1] studied the alkylation and acylation of simple oxindoles, obtaining compounds which were formulated as derivatives of the tautomeric 2-hydroxyindole and 2-hydroxyindolenine forms, but a re-investigation of some of these reactions by Wenkert *et al.*[2,3] has shown that the products thought to be 2-alkoxyindoles are in fact 3-alkyloxindoles. The first authentic 2-alkoxyindoles (I; R = H or Me) were obtained [3] by treating the corresponding 3-hydroxymethyleneoxindoles with ethereal diazomethane, and more recently von Dobeneck and Lehnerer [4] reported the isolation of compounds believed to be (II; R = Me and $CH_2{\cdot}CO_2Me$) on oxidation of ethereal solutions of skatole and methyl 3-indolylacetate respectively with ferric chloride in the presence of secondary aliphatic amines. Compounds (I; R = H and Me) are readily cleaved to the parent oxindoles by dilute alkali, but the product (II; R = Me) is stable to strong aqueous-methanolic potassium hydroxide. It is, however, converted quantitatively by dilute



(I)



(II)



(III)

hydrochloric acid into a mixture of skatole and 3-methyloxindole. The present work has led to the isolation of the first authentic acyl derivatives of a 2-hydroxyindole.

3-Phenyloxindole (III; R = H) was most conveniently prepared by a modification of

[1] Sumpter, *Chem. Rev.*, 1945, **37**, 454; Julian, Meyer, and Printy, in Elderfield, " Heterocyclic Compounds," Wiley and Sons, New York, 1952, Vol. III, p. 126; Sumpter and Miller, in Weissberger, " The Chemistry of Heterocyclic Compounds," Interscience Publ., Inc., New York, 1954, Vol. VIII, p. 134; and references cited therein.
[2] Wenkert, Bose, and Reid, *J. Amer. Chem. Soc.*, 1953, **75**, 5514.
[3] Wenkert, Bhattacharyya, and Reid, *ibid.*, 1956, **78**, 797.
[4] Von Dobeneck and Lehnerer, *Chem. Ber.*, 1957, **90**, 161.

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the procedure described by Meisenheimer and Meis.[5] In the presence of one equivalent of aqueous sodium carbonate it reacted with methyl iodide, benzyl iodide, and phenacyl bromide severally, to yield monosubstitution products which were unchanged by dilute acids or bases and readily gave monoacetates and monobenzoates. These properties suggested that the compounds were (III; R = Me, CH_2Ph, and CH_2Bz). 3-Methyl-3-phenyloxindole was synthesised by Brunner's method[6] from *N*-phenyl-*N*-α-phenylpropionylhydrazine, and was shown (mixed m. p. and ultraviolet spectrum) to be identical with the methylation product of 3-phenyloxindole. An attempt to cyclise *N*-αβ-diphenylpropionyl-*N'*-phenylhydrazine to 3-benzyl-3-phenyloxindole was unsuccessful, but the correctness of this structure for benzylated 3-phenyloxindole was established by its infrared and ultraviolet absorption spectra. The constitution (III; R = CH_2Bz) of the phenacyl derivative was confirmed by the presence of two peaks in the carbonyl region of its infrared spectrum, and the persistence of one of these in the hydrazone (III; R = CH_2·CPh:N·NH_2). 1-Methyl-3-phenyloxindole, obtained in good yield from α-bromo-*N*-methyl-α-phenylacetanilide by Julian and Pikl's modification[7] of Stollé's method,[8] similarly afforded the 3-benzyl derivative when alkylated with benzyl iodide.

1-Benzoyl-3-phenyloxindole was formed when the parent oxindole was treated with benzoic anhydride in the presence[9] of (+)-camphor-10-sulphonic acid or, more conveniently, with benzoyl chloride and aqueous sodium carbonate. The 1-acetyl derivative was obtained[10] by treating 3-phenyloxindole with acetic anhydride alone.

3-Phenyloxindole and its 1-acetyl and 1-benzoyl derivatives dissolve in aqueous sodium hydroxide with, respectively, pale yellow, bright yellow, and orange colours, which may be attributed to the corresponding enol anions. In the last two cases the colours rapidly fade as the acyl groups are hydrolysed, but more stable solutions are formed in aqueous sodium carbonate containing acetone, and addition of methyl or benzyl iodide to these affords the corresponding 1-acyl-3-alkyl-3-phenyloxindoles, identical with those obtained by appropriate acylation of (III; R = Me and CH_2Ph).

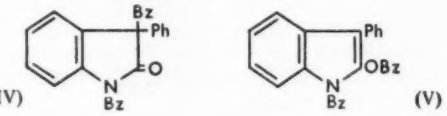
With toluene-*p*-sulphonyl chloride and sodium carbonate, 3-phenyloxindole yielded 3-phenyl-1-toluene-*p*-sulphonyloxindole, whose structure was confirmed by its infrared spectrum. Unlike the 1-acetyl or 1-benzoyl derivative this was extremely resistant to hydrolysis, but gave 3-phenyloxindole quantitatively when treated[11] with Raney nickel in ethanol.

For comparison with 3-phenyl-1-toluene-*p*-sulphonyloxindole, a synthesis of the isomeric sulphone (III; R = *p*-C_6H_4Me·SO_2) was attempted. Treatment of 3-phenyldioxindole (III; R = OH)[12] with thionyl chloride gave 3-chloro-3-phenyloxindole which, with sodium toluene-*p*-sulphinate, afforded 3-phenyl-1-toluene-*p*-sulphonyloxindole, and not the expected sulphone. With aqueous bases, the chloro-compound yielded amorphous material, but it was hydrolysed to the parent dioxindole by water, and with methanol or ethanol it gave the corresponding 3-alkoxy-3-phenyloxindole. In these properties[13] it resembles diphenylmethyl chloride, to which it is formally analogous. 3-Methoxy- and 3-ethoxy-3-phenyloxindole, like 3-phenyldioxindole, dissolve readily in aqueous 5% sodium hydroxide, and may be recovered by acidification.

Benzoylation of 3-phenyloxindole under Schotten–Baumann conditions gave a dibenzoate, which was also obtained on reaction of 1-benzoyl-3-phenyloxindole with benzoic anhydride in the presence of (+)-camphor-10-sulphonic acid. This, together with the fact that both benzoyl groups could be removed by hydrolysis (the 3-acyloxindoles are

[5] Meisenheimer and Meis, *Ber.*, 1924, **57**, 297; cf. Palazzo and Rosnati, *Gazzetta*, 1953, **83**, 211.
[6] Brunner, *Monatsh.*, 1896, **17**, 267, 479.
[7] Julian and Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 563.
[8] Stollé, *J. prakt. Chem.*, 1930, **128**, 1.
[9] Cf. Plant and Tomlinson, *J.*, 1933, 955.
[10] Brunner, *Monatsh.*, 1897, **18**, 547.
[11] Cf. Kenner and Murray, *J.*, 1949, S178.
[12] Kohn, *Monatsh.*, 1910, **31**, 747.
[13] Ward, *J.*, 1927, 2289.

readily hydrolysed [14]), suggested either structure (IV) [15] or (V). The latter was supported by cleavage of the compound to 3-phenyloxindole and benzoylhydrazine when it was treated with ethanolic hydrazine hydrate [16] and by its lack of ketonic activity,[17] and was confirmed by the infrared and ultraviolet absorption spectra. 1-Methyl-3-phenyloxindole similarly afforded 2-benzoyloxy-1-methyl-3-phenylindole. The success of these reactions is probably due to the low solubility of the products.



In the presence of aqueous sodium carbonate, 1-acetyl-3-phenyloxindole with benzoyl chloride gave a good yield of 1-acetyl-2-benzoyloxy-3-phenylindole, but 1-benzoyl-3-phenyloxindole afforded only 2% of the compound (V), and no indole was isolated on reaction with 1-methyl-3-phenyloxindole.

Both 1-acetyl- and 1-benzoyl-3-phenyloxindole afforded the corresponding 1-acyl-2-acetoxy-3-phenylindole when treated with acetic anhydride and (+)-camphor-10-sulphonic acid, but 1-methyl-3-phenyloxindole failed to yield a pure indole.

The infrared absorption maxima in the N–H and C=O stretching regions are given in Tables 1 and 2. Both 3-ethoxy-3-phenyl- and 3-phenyl-1-toluene-*p*-sulphonyl-oxindole have two peaks in the carbonyl region, although they each contain only one carbonyl group. Kellie *et al.*[18] have observed a similar effect in oxindole and some of its simpler

TABLE 1. *Absorption spectra of substituted 3-phenyloxindoles, in Nujol, in the regions 2·8—3·4 and 5·6—6·1 μ.*

Substituent	$\lambda_{max.}$ (μ) *						
None	—	3·15	3·22	—	—	5·82	—
3-Cl	—	3·18	3·25	—	—	5·81	—
3-OH	2·89	3·13	3·26 (m)	—	—	5·88	—
3-OMe	—	3·16	3·23	—	—	5·80	—
3-OEt	—	3·14	(3·23)	—	—	5·79	5·93
3-Me	—	3·18	3·27	—	—	5·87	—
3-CH_2Ph	—	3·13	3·30	—	—	5·89	—
3-CH_2Bz	—	3·13	3·22	3·28	—	5·86	5·89
3-CH_2·CPh:N·NH_2	2·87	(2·99)	3·08	(3·29)	—	5·99	—
1-Me	—	—	—	(3·31) (m)	—	5·89	—
1-Me-3-CH_2Ph	—	—	—	(3·32) (m)	—	5·86	—
1-Bz	—	—	—	—	5·68 (m)	5·90 (m)	—
1-Bz-3-OEt	—	—	—	—	5·67	5·91	—
1-Bz-3-Me	—	—	—	—	5·67	5·92	—
1-Bz-3-CH_2Ph	—	—	—	—	5·77	6·02	—
1-Ac	—	—	—	—	5·65	5·84	—
1-Ac-3-OAc	—	—	3·20 (w)	—	5·66	5·72	5·82
1-Ac-3-Me	—	—	—	—	5·68	5·83	—
1-Ac-3-CH_2Ph	—	—	—	—	5·71	5·83	—
1-Ac-3-CH_2Bz	—	3·12 (w)	—	—	5·72	5·88	5·93
1-*p*-C_6H_4Me·SO_2	—	3·08 (m)	—	—	—	5·80 (m)	5·92 (m)

* Absorption is strong unless stated otherwise. Figures in parentheses indicate shoulders.

derivatives. The 1-acyl-3-phenyloxindoles possess two peaks in the 5·6—6·0 μ region, and these may be attributed either to individual carbonyl absorption or, as suggested by Abramovitch,[19] to vibrational coupling. All the 2-acyloxy-3-phenylindoles show strong

[14] Julian, Magnani, Pikl, and Karpel, *J. Amer. Chem. Soc.*, 1948, **70**, 174.
[15] Cf. Heller and Heine, *Ber.*, 1916, **49**, 2775.
[16] Cf. Curtius and Dellschaft, *J. prakt. Chem.*, 1901, **64**, 419, and preceding papers in the series.
[17] Porter, Robinson, and Wyler, *J.*, 1941, 621.
[18] Kellie, O'Sullivan, and Sadler, *J.*, 1956, 3809.
[19] Abramovitch, *J.*, 1957, 1413.

TABLE 2. *Absorption spectra of substituted 3-phenylindoles, in Nujol, in the regions 2·8—3·0 and 5·6—6·0 μ.*

Substituent	$\lambda_{max.}$ (μ) *			Substituent	$\lambda_{max.}$ (μ) *		
None	2·93 (m)	—	—	1-Bz-2-CH_2Ph	—	—	5·90
2-Me	2·98	—	—	1-Bz-2-OAc	—	5·62	5·92
2-CH_2Ph	2·89 (m)	—	—	1-Bz-2-OBz	—	5·70	5·93
1-Me-2-CH_2Ph	—	—	—	1-Ac	—	—	5·90
1-Me-2-OBz	—	5·73	—	1-Ac-2-Me	—	—	5·91
1-Bz	—	—	5·95	1-Ac-2-OAc	—	5·62 (m)	5·86 (m)
1-Bz-2-Me	—	—	5·91	1-Ac-2-OBz	—	5·67	5·83

* See Table 1.

TABLE 3. *Absorption spectra of substituted 3-phenyloxindoles, in dioxan, in the region 220—400 mμ.*

Substituent	$\lambda_{min.}$ (mμ) *	log ε	$\lambda_{max.}$ (mμ) *	log ε	$\lambda_{min.}$ (mμ) *	log ε	$\lambda_{max.}$ (mμ) *	log ε
None	231	3·81	249	3·96	273	3·12	286	3·22
3-Cl	—	—	(255)	3·76	290	3·06	306	3·15
3-OH	238	3·70	254	3·85	280	3·11	290	3·20
3-OMe	239	3·57	255	3·84	280	3·12	294	3·24
3-OEt	240	3·77	255	3·94	282	3·01	295	3·11
3-Me	233	3·77	250	3·93	275	3·22	283	3·27
3-CH_2Ph	238	3·82	250	3·88	281	3·08	286	3·14
3-CH_2Bz	226	4·17	244	4·34	—	—	(280)	3·55
3-CH_2·CPh:N·NH_2	233	4·09	245	4·16	263	3·93	293	4·18
1-Me	236	3·75	255	4·03	—	—	(283)	3·24
1-Me-3-CH_2Ph	243	3·80	257	3·88	—	—	(288)	3·25
1-Bz	227	4·12	240	4·20	(265)	3·89	(290)	3·61
1-Bz-3-OEt	235	4·15	245	4·19	(270)	3·96	—	—
1-Bz-3-Me	229	4·13	239	4·20	(265)	3·90	(290)	3·64
1-Bz-3-CH_2Ph	231	4·18	240	4·23	—	—	(290)	3·55
1-Ac	(230)	4·09	—	—	—	—	—	—
1-Ac-3-OAc	—	—	—	—	—	—	—	—
1-Ac-3-Me	(233)	4·08	—	—	—	—	—	—
1-Ac-3-CH_2Ph	—	—	—	—	—	—	—	—
1-Ac-3-CH_2Bz	224	4·29	240	4·41	—	—	—	—
1-*p*-C_6H_4Me·SO_2	—	—	228	4·54	287	3·25	295	3·34

* Figures in parentheses indicate the approximate centre of a pronounced shoulder.

TABLE 4. *Absorption spectra of substituted 3-phenylindoles, in dioxan, in the region 220—400 mμ.*

Substituent	$\lambda_{min.}$ (mμ)	log ε	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)	log ε	λ_{max} (mμ) *	log ε	$\lambda_{min.}$ (mμ)	log ε	$\lambda_{max.}$ (mμ)	log ε
None	—	—	225	4·50	245	3·73	270	4·18	—	—	—	—
2-Me	—	—	228	4·53	247	3·75	279	4·19	—	—	—	—
2-CH_2Ph	—	—	228	4·59	249	3·89	282	4·22	—	—	—	—
1-Me-2-CH_2Ph	—	—	231	4·59	249	3·89	285	4·17	—	—	—	—
1-Me-2-OBz	—	—	232	4·66	252	4·03	275	4·25	—	—	—	—
1-Bz	—	—	227	4·53	245	4·28	258	4·34	294	3·81	310	3·96
1-Bz-2-Me	—	—	228	4·55	251	4·25	266	4·28	301	3·67	318	3·74
1-Bz-2-CH_2Ph	—	—	228	4·58	250	4·23	266	4·30	301	3·67	319	3·75
1-Bz-2-OAc	—	—	225	4·50	—	—	(255)	4·31	295	3·74	313	3·82
1-Bz-2-OBz	—	—	230	4·63	—	—	(260)	4·37	297	3·82	313	3·89
1-Ac	224	4·27	246	4·40	—	—	—	—	284	3·89	305	4·08
1-Ac-2-Me	230	4·18	246	4·33	—	—	—	—	292	3·85	303	3·91
1-Ac-2-OAc	229	4·25	245	4·00	—	—	—	—	287	3·93	301	4·00
1-Ac-2-OBz	—	—	238	4·57	—	—	—	—	291	4·02	301	4·05

* See Table 3.

or medium absorption at 5·6—5·75 μ, which is characteristic [20] of a carbonyl group in the system CO·O·C:C, and this confirms the structures assigned to the compounds.

The main features of the ultraviolet absorption spectra are shown in Tables 3 and 4. The introduction of a 1-acetyl group has a pronounced effect on the spectra of both classes of compound, and in the oxindole series causes complete suppression of the peaks in all cases except that of 3-phenacyl-3-phenyloxindole, where the persistence of a maximum may be attributed to the phenacyl group. In the 220—300 mμ region the spectra of the 2-acyloxy-3-phenylindoles are very similar to those of similarly substituted 3-phenylindole reference compounds, whose preparations are described in the Experimental section. Tailing of the absorption into the visible region accounts for the yellowish colour of several of the benzoyl derivatives.

Experimental

Solutions in organic solvents were dried with sodium sulphate. Solvents, and reagents present in excess, were removed on the water-bath, where necessary under reduced pressure (water-pump). Solids were dried *in vacuo*. Sublimation temperatures are those of the heating-bath. Sodium carbonate refers to "AnalaR" anhydrous material. Reagents were purified by conventional procedures. M. p.s are corrected.

A. Derivatives of 3-Phenyloxindole.

3-Phenyloxindole.—(*a*) Powdered (±)-mandelanilide [21] (57 g.) was added during 5 min. to vigorously stirred concentrated sulphuric acid (300 c.c.) at 20—25°, stirring was continued for 10 min., and the solution was added to crushed ice (2 kg.). After 2 hr. the precipitate was collected, washed with water, and crystallised from ethanol to give a solid which, on being sublimed at 180°/0·01 mm., afforded the oxindole (37 g., 71%) as needles, m. p. 191° undepressed on admixture with material prepared by method (*b*) or (*c*) (lit.,[5, 10, 22] 183°, 185—187°) (Found: C, 80·4; H, 5·4; N, 6·7. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3; N, 6·7%).

(*b*) A mixture of 3-phenyldioxindole [12] (10 g.), stannous chloride (20 g.; "AnalaR"), acetic acid (50 c.c.), and concentrated hydrochloric acid (50 c.c.) was refluxed for 1½ hr. (addition of porous plate to prevent bumping lowers the yield), diluted with water (100 c.c.), and cooled to room temperature. The resulting microcrystalline powder (9 g., 97%) had m. p. 188—189°, which was raised to 192° by sublimation at 180°/0·01 mm. and crystallisation from ethanol.

(*c*) *N*-Phenylacetyl-*N'*-phenylhydrazine (2·25 g.) was cyclised [10] with calcium oxide (10 g.) as described below for 3-methyl-3-phenyloxindole, giving 3-phenyloxindole (80 mg., 4%), m. p. 190—191°.

α-Bromophenylacetic Acid.—To a stirred mixture of 48% hydrobromic acid (85 c.c.) and concentrated sulphuric acid (21 c.c.) were added successively (±)-mandelic acid (59 g.) and sulphuric acid (21 c.c.), and the solution was stirred, under reflux, at 125—130° for 3 hr., cooled, and added to water (300 c.c.). The precipitate was isolated by extraction with ether, and distilled, giving an oil, b. p. 120—121°/0·02 mm., which largely solidified and, on being crystallised from light petroleum (b. p. 60—80°), afforded the acid (62 g., 74%) as prisms, m. p. 68—69° (lit.,[23] in the range 82—84°) (Found: Br, 37·9. Calc. for $C_8H_7O_2Br$: Br, 37·2%). The amide, needles (from xylene), had m. p. 147° (lit.,[24] 144°, 146°) (Found: N, 6·5; Br, 37·6. Calc. for C_8H_8ONBr: N, 6·5; Br, 37·4%).

1-Methyl-3-phenyloxindole.—α-Bromophenylacetic acid (54 g.) was refluxed (water-bath) with thionyl chloride (45 c.c.) for 5 hr., the excess of reagent was removed, and the residue, in benzene (50 c.c.), was added during 30 min. to a cooled (ice-bath) and vigorously stirred solution of *N*-methylaniline (54 g.) in benzene (75 c.c.). The mixture was stirred at room temperature for 30 min., heated to the b. p., and cooled to 5°. The solid was removed and rinsed with cold benzene, and the filtrate was washed with 5% hydrochloric acid containing 5% of sodium

[20] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 156, and references cited therein.
[21] Bischoff and Walden, *Annalen*, 1894, **279**, 123.
[22] Marschalk, *Bull. Soc. chim. France*, 1952, 949.
[23] Alexander, *Annalen*, 1890, **258**, 70; Tillmanns, *ibid.*, p. 88; Hell and Weinzweig, *Ber.*, 1895, **28**, 2447; Darapsky, *J. prakt. Chem.*, 1917, **96**, 285.
[24] Opolski and Weinbaum, *Ber.*, 1914, **47**, 1561; Fourneau and Nicolitch, *Bull. Soc. chim. France*, 1928, **43**, 1251.

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chloride, then with aqueous 5% sodium chloride, and dried. Removal of the solvent and distillation of the residue gave crude *α-bromo-N-methyl-α-phenylacetanilide* (45 g.), b. p. 171—172°/0·03 mm. with slight decomposition. A mixture of this anilide (40·5 g.) and powdered anhydrous aluminium chloride (36 g.) was stirred and cautiously warmed (water-bath) until evolution of hydrogen bromide commenced. The vigorous reaction was moderated by water-cooling, and, when it had subsided, the mixture was stirred for 30 min. in a metal-bath at 175—180°. The melt was cooled, powdered, and slowly added to crushed ice (500 g.) and water (100 c.c.), and the suspension was stirred for 30 min. Concentrated hydrochloric acid (100 c.c.) was added, stirring was continued for 30 min., and the temperature raised to 60° to coagulate the precipitate which, after being cooled to 15°, was collected, washed with water, and crystallised (charcoal) from ethanol. Sublimation of the product at 115°/0·01 mm., and crystallisation of the sublimate from light petroleum (b. p. 100—120°), afforded the *oxindole* (23·5 g.) as needles, m. p. 119·5° (Found: C, 80·5; H, 5·9; N, 6·3. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%). The oxindole was recovered [25] after being refluxed for 24 hr. with an excess of anhydrous pyridine hydrochloride.

Alkylation Experiments.—The alkyl halide (0·011 mole) in acetone (15 c.c.) was added to a mixture of the powdered oxindole (0·01 mole), sodium carbonate (0·53 g.), acetone (10 c.c.), and water (10 c.c.), and the solution was stirred and refluxed for the period indicated below, cooled, and added to water (200 c.c.). The precipitate was collected, washed with water, dried, and triturated with a little cold light petroleum (b. p. 60—80°). It was then sublimed at 0·01 mm., and the sublimate was crystallised. The following *3-phenyloxindoles* were prepared by alkylation with methyl or benzyl iodide, or phenacyl bromide, of the corresponding oxindole; the reflux period, yield, and solvent used for crystallisation are indicated, in that order, in parentheses: 3-Methyl- * (6 hr., 63%, aq. MeOH), blades, m. p. 155—155·5° (Found: C, 80·6; H, 5·7; N, 6·5. Calc. for $C_{15}H_{13}ON$: C, 80·7; H, 5·8; N, 6·3%). *3-Benzyl-* (6 hr., 83%, MeOH), tablets, m. p. 158° (Found: C, 84·0; H, 5·6; N, 5·0. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%). *3-Phenacyl-* (4 hr., 62%, Bu^nOH), prisms, m. p. 203·5—204° (Found: C, 80·5; H, 5·1; N, 4·3. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%). *1-Acetyl-3-methyl-* (3 hr., 67%, EtOH), prisms, m. p. 113° (Found: C, 76·7; H, 5·6; N, 5·0. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%). *1-Acetyl-3-benzyl-* (1 hr., 93%, aq. EtOH), blades, m. p. 139° (Found: C, 81·0; H, 5·3; N, 4·4. $C_{23}H_{19}O_2N$ requires C, 80·9; H, 5·6; N, 4·1%). *1-Acetyl-3-phenacyl-* (4 hr., 62%, EtOH), needles, m. p. 163·5—164° (Found: C, 78·3; H, 5·3; N, 4·1. $C_{24}H_{19}O_3N$ requires C, 78·0; H, 5·2; N, 3·8%). *1-Benzoyl-3-benzyl-* (15 min., 89%, EtOH), tablets, m. p. 154° (Found: C, 83·5; H, 5·1; N, 3·7. $C_{28}H_{21}O_2N$ requires C, 83·4; H, 5·2; N, 3·5%). *3-Benzyl-1-methyl-* (5 hr., 96%, MeOH), prisms, m. p. 127—127·5° (Found: C, 84·3; H, 6·0; N, 4·5. $C_{22}H_{19}ON$ requires C, 84·4; H, 6·1; N, 4·5%).

N-Phenyl-N′-α-phenylpropionylhydrazine.—A mixture of α-phenylpropionic acid [26] (7·5 g.), phenylhydrazine (5·5 g.), and benzene (60 c.c.) was refluxed under an azeotropic water-separator for 18 hr., the solvent was removed, and the residue was distilled. Crystallisation of the fraction with b. p. 170—175°/0·02 mm. from light petroleum (b. p. 80—100°) gave the *hydrazine* (6 g., 50%) as stout needles, m. p. 85·5—86° (Found: C, 75·3; H, 6·5; N, 12·0. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%). The compound separated from aqueous methanol as needles, m. p. 99—100°, and a mixture of the two forms partially melted at 86°, solidified at 90°, and then had m. p. 99—100°. The latter species was converted into the form of low m. p. by crystallisation from light petroleum.

3-Methyl-3-phenyloxindole.—An intimate mixture of the foregoing hydrazine (1·2 g.) and freshly ignited calcium oxide (6 g.) was heated at 210—215° (metal-bath) in a slow stream of oxygen-free nitrogen for 4 hr., cooled, powdered, and added, below 20°, to 10% hydrochloric acid (75 c.c.). The resulting gum was isolated by extraction with ether and sublimed at 155°/0·01 mm., and the sublimate was crystallised from aqueous methanol to give a solid which, after being dried, was triturated with a little cold light petroleum (b. p. 60—80°) and sublimed, in a vertical tube, at 145°/0·01 mm. until the molten residue was no longer turbid; two bands were formed. The lower was crystallised first from benzene–light petroleum (b. p. 40—60°),

* A specimen of 3-methyl-3-phenyloxindole prepared from (±)atrolactanilide, and kindly supplied by Dr. E. F. M. Stephenson (*J.*, 1957, 1928) was identical in crystalline form, mixed m. p., and infrared spectrum with this compound. The solubility in aqueous 10% sodium hydroxide at 60° is *ca.* 0·3%.

[25] Cf. Klamann and Schaffer, *Chem. Ber.*, 1954, **87**, 1294.

[26] Hauser and Brasen, *J. Amer. Chem. Soc.*, 1956, **78**, 494.

and then from aqueous methanol, to give the oxindole (75 mg., 7%) as slender blades, m. p. 156° undepressed on admixture with material prepared by methylation of 3-phenyloxindole (Found: C, 81·0; H, 5·9; N, 6·6%).

N-αβ-*Diphenylpropionyl*-N'-*phenylhydrazine*.—αβ-Diphenylpropionyl chloride [27] (7·4 g.), in ether (50 c.c.), was added at 0—5° during 30 min. to a vigorously stirred solution of phenylhydrazine (6·5 g.) in ether (75 c.c.), and the suspension was stirred at room temperature for 1½ hr. Benzene (200 c.c.) and water (150 c.c.) were added, stirring was continued until the solid had dissolved, and the organic phase was removed, washed with water, and dried. Removal of the solvent left a residue which, on being triturated with a little cold ether and crystallised from aqueous methanol, gave the *hydrazine* (7·8 g., 82%) as needles, m. p. 139·5—140·5° (Found: C, 79·8; H, 6·4; N, 9·2. $C_{21}H_{20}ON_2$ requires C, 79·8; H, 6·3; N, 8·9%).

3-*Phenacyl*-3-*phenyloxindole Hydrazone*.—3-Phenacyl-3-phenyloxindole (3·3 g.), 99—100% hydrazine hydrate (6 c.c.), and ethanol (30 c.c.) were stirred and refluxed for 10 hr., the solvent and excess hydrazine were removed, and the residue was washed with water and boiled for 5 min. with methanol (100 c.c.). The hot suspension was filtered; the solid was rinsed with hot methanol and crystallised from butan-1-ol, to give the *hydrazone* (0·8 g., 23%) as needles, m. p. 208—209° (Found: C, 77·6; H, 5·6; N, 12·5. $C_{22}H_{19}ON_3$ requires C, 77·4; H, 5·6; N, 12·3%). The compound was readily hydrolysed to the parent ketone by dilute hydrochloric acid. An attempted preparation of 3-phenethyl-3-phenyloxindole by the Wolff–Kishner method was unsuccessful.

1-*Acetyl*-3-*phenyloxindoles*.—The oxindole was refluxed for 3 hr. with an excess of acetic anhydride, the reagent was removed, and the residue was crystallised from ethanol. The yield of 1-acetyl-3-phenyloxindole was markedly reduced by traces of impurities in the reagents, and the derivative was conveniently purified by short-path distillation at 140°/0·02 mm. before crystallisation. The following 1-*acetyl*-3-*phenyloxindoles* were prepared, the yield being indicated in parentheses: Unsubstituted (36—61%), needles, m. p. 106° (lit.,[10] 103°) (Found: C, 76·5; H, 5·3; N, 5·6; Ac, 18·0. Calc. for $C_{16}H_{13}O_2N$: C, 76·5; H, 5·2; N, 5·6; Ac, 17·1%). 3-Acetoxy- (76%), needles, m. p. 142° (lit.,[28] 140—141°) (Found: C, 69·9; H, 4·8; N, 4·5. Calc. for $C_{18}H_{15}O_4N$: C, 69·9; H, 4·9; N, 4·5%). For 3-methyl- (75%), 3-benzyl- (98%), and 3-phenacyl- (84%), see "Alkylation Experiments."

1-*Benzoyl*-3-*phenyloxindoles*.—(*a*) 3-Methyl-3-phenyloxindole (0·45 g.) and benzoic anhydride (0·6 g.) were heated in a metal-bath at 190—200° for 4 hr., the sublimate of benzoic acid was removed, and the residue was crystallised from ethanol, to give 1-*benzoyl*-3-*methyl*-3-*phenyloxindole* (0·46 g., 71%) as prisms, m. p. 136—136·5° (Found: C, 80·7; H, 5·1; N, 4·4. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%). The derivative is dimorphic, with a metastable form of m. p. 122·5°. The corresponding 3-benzyl compound (yield 74%) was identical with that prepared by benzylation of 1-benzoyl-3-phenyloxindole, but a metastable form, m. p. 120°, was also obtained.

(*b*) 3-Phenyloxindole (0·21 g.), benzoic anhydride (1 g.), and (+)-camphor-10-sulphonic acid (5 mg.) were heated together for 2 hr. in a metal-bath at 180—185°, the sublimate was removed, and the residue was twice crystallised from ethanol. Sublimation of the product at 170°/0·01 mm. and crystallisation of the sublimate from ethanol afforded 1-*benzoyl*-3-*phenyloxindole* (37 mg., 9%) as felted needles, m. p. 175·5° (Found: C, 80·7; H, 4·8; N, 4·8; Bz, 35·1. $C_{21}H_{15}O_2N$ requires C, 80·5; H, 4·8; N, 4·5; Bz, 33·6%).

(*c*) A mixture of 3-phenyloxindole (4·2 g.), sodium carbonate (5·3 g.), water (40 c.c.), and acetone (40 c.c.) was refluxed until the solids had dissolved, and to the boiling solution, vigorously stirred, was added during 1 min. benzoyl chloride (14 g.) in acetone (20 c.c.). Refluxing was continued for 15 min., the mixture was cooled and added to water (400 c.c.), and, after several hours at room temperature, the semisolid precipitate was isolated by decantation, washed with water, and extracted with cold benzene. The extract, after being dried and concentrated to 50 c.c., was stirred and diluted by the dropwise addition of light petroleum (200 c.c.; b. p. 60—80°), and the precipitate was collected, washed with light petroleum, and sublimed at 180°/0·01 mm. Crystallisation of the sublimate from ethanol gave needles (1·75 g., 28%), m. p. 175·5° undepressed on admixture with 1-benzoyl-3-phenyloxindole prepared by method (*b*).

(*d*) 1-*Benzoyl*-3-*ethoxy*-3-*phenyloxindole*, prepared in 63% yield by the Schotten–Baumann

[27] Rupe and Kerkovins, *Ber.*, 1912, **45**, 1401.
[28] Inagaki, *J. Pharm. Soc. Japan*, 1939, **59**, 5.

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method, formed prisms (from ethanol), m. p. 130—130·5° (Found: C, 77·4; H, 5·3; N, 4·0. $C_{23}H_{19}O_3N$ requires C, 77·3; H, 5·3; N, 3·9%).

3-*Phenyl*-1-*toluene*-p-*sulphonyloxindole*.—(*a*) A mixture of 3-phenyloxindole (10·4 g.), toluene-*p*-sulphonyl chloride (9·6 g.), sodium carbonate (3·75 g.), water (50 c.c.), and acetone (100 c.c.) was stirred and refluxed for 40 min., and the hot suspension was filtered. The solid was washed with 50% aqueous acetone, then with methanol, and crystallised from butan-1-ol, to give the *acyloxindole* (7·5 g., 41%) as felted needles, m. p. 244·5° (decomp.) (Found: C, 69·2; H, 4·5; N, 4·0; S, 8·8. $C_{21}H_{17}O_3NS$ requires C, 69·4; H, 4·7; N, 3·9; S, 8·8%).

(*b*) 3-Chloro-3-phenyloxindole (0·59 g.) was added to a solution of sodium toluene-*p*-sulphinate (2·14 g.) in ethanol–water (15 + 5 c.c.), and the mixture was refluxed for 1 hr., and cooled. The precipitate was collected, washed with 50% aqueous ethanol, dried, and crystallised from butan-1-ol, giving needles (0·35 g., 48%), m. p. 242—243° (decomp.) undepressed on admixture with material prepared by method (*a*).

Cleavage of 3-*Phenyl*-1-*toluene*-p-*sulphonyloxindole*.—A mixture of the oxindole (0·365 g.), Raney nickel [29] (2 g.), and ethanol (20 c.c.) was stirred and refluxed for 6 hr., and filtered. The nickel residues were washed with boiling ethanol, and the combined filtrate and washings were evaporated, leaving a powder (0·209 g., 100%), m. p. 192° undepressed on admixture with 3-phenyloxindole.

3-*Chloro*-3-*phenyloxindole*.—3-Phenyldioxindole [11] (4·5 g.) was refluxed with thionyl chloride (30 c.c.) for 1½ hr., the excess of reagent was removed, and the residue was dissolved in hot benzene (10 c.c.). The solution was slowly diluted with light petroleum (100 c.c.; b. p. 40—60°) and, after several hours at room temperature, the precipitate (3·25 g., 67%) was collected, washed with light petroleum, and dried. It had m. p. 137—139° (decomp.), and was used for preparative purposes without purification. For analysis and spectra, a portion (1·5 g.) was extracted for 15 min. with boiling light petroleum (50 c.c.; b. p. 100—120°), the extract was stirred at room temperature for several hours, and the solid was collected and sublimed at 135°/0·01 mm. until the residue became light brown and began to sinter. The sublimate was washed with cold light petroleum (b. p. 60—80°) and dried, giving the *oxindole* (0·36 g.) as irregular prisms, m. p. 146·5—147·5° (decomp.) (Found: C, 69·3; H, 4·3; N, 5·6; Cl, 14·9. $C_{14}H_{10}ONCl$ requires C, 69·0; H, 4·1; N, 5·8; Cl, 14·6%).

Reactions of 3-*Chloro*-3-*phenyloxindole*.—(*a*) Water (10 c.c.) at 80° was added to a solution of the oxindole (0·1 g.) in dioxan (2 c.c.), the suspension was heated on the water-bath for 15 min., and most of the solvent was removed. Sublimation of the residual solid at 190°/0·01 mm. and crystallisation of the sublimate from aqueous ethanol afforded 3-phenyldioxindole (54 mg., 50%) as needles, m. p. 213—213·5° undepressed by authentic [11] material.

(*b*) A solution of the oxindole (0·73 g.) in methanol (10 c.c.) was boiled for 2 min., diluted with water (25 c.c.) at 50°, and left overnight at room temperature. The precipitate was collected, washed with water, and sublimed at 160°/0·01 mm., and the sublimate was crystallised from aqueous methanol to give 3-*methoxy*-3-*phenyloxindole* (0·67 g., 93%), blades, m. p. 173·5° (Found: C, 75·5; H, 5·4; N, 5·9. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%).

(*c*) Experiment (*b*) was repeated, ethanol being used. 3-*Ethoxy*-3-*phenyloxindole* (88%) formed blades (from aqueous ethanol), m. p. 169—169·5° (Found: C, 75·6; H, 5·9; N, 5·5. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9; N, 5·5%).

B. Derivatives of 2-*Hydroxy*-3-*phenylindole.*

1-*Benzoyl*-2-*benzoyloxy*-3-*phenylindole*.—To a mixture of 3-phenyloxindole (8·4 g.) in acetone (100 c.c.), and sodium hydroxide (45 g.) in water (500 c.c.) at 20° was added, all at once, benzoyl chloride (20 c.c.), and the suspension was vigorously stirred for 15 min. The precipitate was collected, washed with water, and crystallised from glacial acetic acid. Sublimation of the product at 185°/0·01 mm. and crystallisation of the sublimate from ethanol–butan-1-ol (3 : 1) gave the *acyloxy-indole* (7·2 g., 43%) as very pale green hexagonal plates, m. p. 189°, which were markedly thermochromic (Found: C, 80·3; H, 4·5; N, 3·6; Bz, 48·6. $C_{28}H_{19}O_3N$ requires C, 80·6; H, 4·6; N, 3·4; Bz, 50·4%). This indole was also formed, in 4% yield, when 1-benzoyl-3-phenyloxindole (0·31 g.) was heated at 180—185° for 2 hr. with benzoic anhydride (1 g.) and (+)-camphor-10-sulphonic acid (5 mg.), and in 2% yield when it was treated with benzoyl chloride in the presence of one equivalent of sodium carbonate in aqueous acetone.

Cleavage of 1-*Benzoyl*-2-*benzoyloxy*-3-*phenylindole*.—The indole (0·83 g.) was stirred and

[29] Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013.

refluxed for 8 hr. with a mixture of 99—100% hydrazine hydrate (1·2 c.c.) and ethanol (10 c.c.), then the solvent and excess of reagent were removed, and the residue was dissolved in methanol (10 c.c.). Water (20 c.c.) was added and, after 5 hr. at room temperature, the precipitate was collected (filtrate " A "), washed with water, dried, and triturated with cold ether (2 c.c.). Sublimation of the ether-insoluble material at 180°/0·02 mm. gave 3-phenyloxindole (0·21 g., 50%), m. p. and mixed m. p. 190·5—191°. Removal of the solvent from " A " and crystallisation of the residue from benzene afforded benzoylhydrazine (0·4 g., 74%) as blades, m. p. 112·5—113° (lit.,[30] 112·5°) (Found: N, 20·5. Calc. for $C_7H_8ON_2$: N, 20·6%).

2-*Benzoyloxy*-1-*methyl*-3-*phenylindole*.—To aqueous 10% sodium hydroxide (50 c.c.) were added successively 1-methyl-3-phenyloxindole (1·1 g.) in acetone (10 c.c.), and benzoyl chloride (2 c.c.), and the suspension was vigorously stirred for 30 min. The precipitate was collected, washed with water, and crystallised from ethanol, and the product was sublimed at 160°/0·01 mm. Crystallisation of the sublimate from ethanol gave the *acyloxy-indole* (0·52 g., 32%) as very pale yellowish-green blades, m. p. 161·5° (Found: C, 80·4; H, 5·4; N, 4·5; Bz, 30·6. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3; Bz, 32·1%).

1-*Acetyl*-2-*benzoyloxy*-3-*phenylindole*.—A mixture of 1-acetyl-3-phenyloxindole (2·5 g.), sodium carbonate (0·53 g.), acetone (20 c.c.), and water (10 c.c.) was rapidly heated to the b. p., and to it, with vigorous stirring, was added during 15 sec. benzoyl chloride (1·4 g.) in acetone (10 c.c.). The suspension was stirred and refluxed for 15 min., cooled, and added to water (200 c.c.). After 2 hr. the precipitate was collected, washed with water, dried, and triturated with a little light petroleum (b. p. 60—80°). Crystallisation from ethanol, sublimation at 180°/0·01 mm., and recrystallisation of the sublimate from ethanol gave the *indole* (1·98 g., 56%) as irregular rhombic plates, m. p. 184·5° (Found: C, 78·1; H, 5·0; N, 4·1; Ac + Bz, 42·4. $C_{23}H_{17}O_3N$ requires C, 77·8; H, 4·8; N, 3·9; Ac + Bz, 41·7%).

2-*Acetoxy*-1-*acetyl*-3-*phenylindole*.—1-Acetyl-3-phenyloxindole (1·26 g.), (+)-camphor-10-sulphonic acid (25 mg.), and acetic anhydride (25 c.c.) were stirred and refluxed for 6 hr., then the solvent was removed; the residue crystallised from methanol (8 c.c.) as prisms (0·43 g.), m. p. 103·5—104° undepressed by starting material. The mother-liquors were evaporated, and the residue was powdered and extracted with boiling light petroleum (2 × 8 c.c.; b. p. 60—80°). Sublimation of the insoluble material at 170°/0·01 mm. and crystallisation of the sublimate from ethanol gave 3-phenyloxindole (0·43 g.) as prisms, m. p. and mixed m. p. 190·5—191°. The light petroleum extracts were combined, concentrated to 8 c.c., and cooled; the solid which separated was distilled at 0·01 mm. (heating-bath at 120°). Crystallisation of the distillate, which solidified, from light petroleum (b. p. 60—80°) afforded the *indole* (56 mg., 4%) as needles, m. p. 111·5—112° (Found: C, 73·5; H, 5·0; N, 4·8; Ac, 29·2. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1; N, 4·8; Ac, 29·4%).

2-*Acetoxy*-1-*benzoyl*-3-*phenylindole*.—A mixture of 1-benzoyl-3-phenyloxindole (0·63 g.), (+)-camphor-10-sulphonic acid (10 mg.), and acetic anhydride (10 c.c.) was stirred and refluxed for 6 hr., the solvent was removed, and the residue was crystallised three times from ethanol (15, 10, 25 c.c.). Sublimation of the product at 145°/0·01 mm., and crystallisation of the sublimate from ethanol gave the *indole* (0·13 g., 18%) as very pale green needles, m. p. 153° (Found: C, 77·7; H, 4·7; N, 4·1; Ac + Bz, 43·0. $C_{23}H_{17}O_3N$ requires C, 77·8; H, 4·8; N, 3·9; Ac + Bz, 41·7%).

C. Substituted 3-*Phenylindoles.*

Derivatives of 3-*Phenylindole*.—(*a*) 3-Phenylindole[31] (0·58 g.), anhydrous sodium acetate (1·5 g.), and acetic anhydride (15 c.c.) were stirred and refluxed for 3 hr., the solvent was removed, and the residue was triturated with water (3 × 10 c.c.), and dried. Sublimation at 150°/0·02 mm. and crystallisation of the sublimate from ethanol gave 1-*acetyl*-3-*phenylindole* (0·58 g., 82%) as hexagonal plates, m. p. 138·5—139° (Found: C, 81·7; H, 5·6; N, 5·9. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

(*b*) Benzoyl chloride (5 c.c.) was added all at once to a vigorously stirred mixture of 3-phenylindole (0·97 g.), acetone (15 c.c.), and aqueous 20% potassium hydroxide (50 c.c.), stirring was continued for 15 min., and the suspension was diluted with water (100 c.c.) and stirred for 15 min. more. The precipitate, washed with water and dried, was crystallised from butan-1-ol, and the product was sublimed at 160°/0·01 mm. Crystallisation of the sublimate from

[30] Curtius and Struve, *J. prakt. Chem.*, 1894, **50**, 295.
[31] Fischer and Schmidt, *Ber.*, 1888, **21**, 1811.

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butan-1-ol afforded 1-*benzoyl*-3-*phenylindole* (1·2 g., 81%) as blades, m. p. 156·5° (Found: C, 85·0; H, 4·8; N, 4·7. $C_{21}H_{15}ON$ requires C, 84·8; H, 5·1; N, 4·7%).

Derivatives of 2-*Methyl*-3-*phenylindole*.—(*a*) 2-Methyl-3-phenylindole (0·62 g.) [m. p. 61—61·5° (lit.,[32] 59—60°)] in ether (10 c.c.) was added during 5 min. to a stirred solution of methylmagnesium iodide (0·55 g.) in ether (5 c.c.), the mixture was refluxed for 1 hr., then cooled to 15°, and to it was added, dropwise with vigorous stirring, acetyl chloride (0·25 g.) in ether (5 c.c.). After being refluxed for 1 hr. the suspension was cooled, ammonium chloride (1 g.) in water (10 c.c.) was added, and the ethereal phase was separated, washed with water, and dried. The solvent was removed, the residue was crystallised from ethanol, and the product was sublimed at 125°/0·01 mm. Crystallisation of the sublimate from ethanol gave 1-*acetyl*-2-*methyl*-3-*phenylindole* (0·3 g., 40%) as rhombic tablets, m. p. 119° (Found: C, 81·7; H, 5·9; N, 5·4. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0; N, 5·6%). The derivative also separated from ethanol as rods, m. p. 119° undepressed on admixture with the rhombic form. The species were spectroscopically identical.

(*b*) Experiment (*a*) was repeated, but with benzoyl chloride (0·42 g.). The crude product was crystallised from butan-1-ol and sublimed at 160°/0·02 mm. 1-*Benzoyl*-2-*methyl*-3-*phenylindole* (0·6 g., 64%) formed pale yellowish-green prisms (from butan-1-ol), m. p. 152° (Found: C, 85·2; H, 5·5; N, 4·3. $C_{22}H_{17}ON$ requires C, 84·9; H, 5·5; N, 4·5%).

1-*Benzoyl*-2-*benzyl*-3-*phenylindole*.—Ethereal 2-benzyl-3-phenylindolylmagnesium iodide, from the indole (0·85 g.) [m. p. 101·5—102° (lit.,[32] 100—101°)], was reacted with benzoyl chloride (0·42 g.) as described for the 2-methyl-compound, but the reflux period was 2 hr. The crude product was crystallised successively from ethanol and butan-1-ol, and then sublimed at 170°/0·01 mm. until the residue solidified. Crystallisation of the sublimate from butan-1-ol, resublimation at 160°/0·01 mm., and recrystallisation from butan-1-ol gave the *indole* (0·23 g., 20%) as pale greenish-yellow blades, m. p. 164·5° (Found: C, 86·7; H, 5·2; N, 3·5. $C_{28}H_{21}ON$ requires C, 86·8; H, 5·4; N, 3·6%). Attempts to prepare 1-acetyl-2-benzyl-3-phenylindole were unsuccessful.

2-*Benzyl*-1-*methyl*-3-*phenylindole*.—This was purified by sublimation at 120°/0·01 mm. Crystallisation of the sublimate from glacial acetic acid gave colourless rhombic plates, m. p. 122° (lit.,[33] straw-yellow, m. p. 129—130°) (Found: N, 4·5. Calc. for $C_{22}H_{19}N$: N, 4·7%).

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[*Received, June 4th,* 1957.]

[32] Trenkler, *Annalen*, 1888, **248**, 106.
[33] Neber, Knöller, Herbst, and Trissler, *ibid.*, 1929, **471**, 113.

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967. 3-*Formyl*cyclo*hexane*spirocyclo*pentane*-2 : 4-*dione and* 2-*Formyl*-5 : 5-*dimethyl*cyclo*hexane*-1 : 3-*dione*.

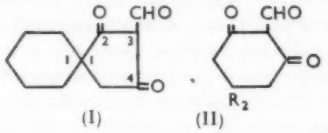
By B. D. AKEHURST and J. R. BARTELS-KEITH.

3-Formyl*cyclo*hexane*spirocyclo*pentane-2 : 4-dione and 2-formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione have been synthesised, and their ultraviolet and infrared absorption spectra studied and compared with those of 3-formylpentane-2 : 4-dione. Derivatives and degradative experiments are reported for the two new compounds, and 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-9-(2-hydroxy-4 : 4-dimethyl-6-oxo*cyclo*hex-1-enyl)-3 : 3 : 6 : 6-tetramethyl-1 : 8-dioxoxanthen has been obtained by the action of dimedone on 2-formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione.

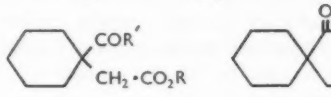
2-ACYL-1 : 3-DIKETONES have interest particularly since several have biological activity. Two acyclic examples, 3-formylpentane-2 : 4-dione[1] and triacetylmethane,[2] have long been known, and many cyclic 2-acyl-1 : 3-diketones have been isolated from natural sources (for references see Chan and Hassall[3]).

[1] Claisen, *Ber.*, 1893, **26**, 2731.
[2] Nef, *Annalen*, 1893, **277**, 71.
[3] Chan and Hassall, *J.*, 1956, 3495.

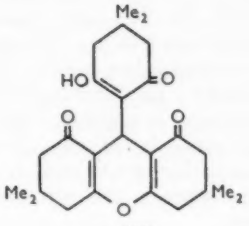
Although several 2-acyl-1 : 3-diketones have been described, 2-formyl-1 : 3-diketones have not been studied systematically. The present paper records the synthesis of 3-formyl-*cyclo*hexane*spirocyclo*pentane-2 : 4-dione (I) and 2-formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (II; R = Me). Condensation of 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione with ethyl orthoformate in the presence of acetic anhydride, followed by alkaline hydrolysis, gave the formyl-diketone (II; R = Me), with comparable amounts of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-9-(2-hydroxy-4 : 4-dimethyl-6-oxo*cyclo*hex-1-enyl)-3 : 3 : 6 : 6-tetramethyl-1 : 8-dioxoxanthen [4] (III). Formation of the xanthen (III) by the action of ethyl orthoformate on 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione has been noted previously.[5]



(I) (II)



(IV) (V)



(III)

Unlike 2-formyl*cyclo*hexane-1 : 3-dione (II; R = H) which Rogers and Smith [6] obtained only as an unstable oil, 2-formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (II; R = Me) is crystalline (m. p. 77°) and readily dissolves in common solvents. It behaved as a monobasic acid (p*K* 3·65) and gave an intense orange colour with ferric chloride, a crimson colour with titanous chloride [7] in methanol (transient green in the presence of pyridine), and a blue crystalline copper complex. Like 2-formyl*cyclo*hexane-1 : 3-dione [6] (II; R = H), it readily gave a crystalline anil. On oxidation with alkaline hydrogen peroxide it gave formic acid and ββ-dimethylglutaric acid, and on acid hydrolysis it gave the condensation product (III). The latter was also obtained, in good yield, on condensation of the formyl-diketone (II; R = Me) with 2 mols. of dimedone, which confirms the structure (III) [4, 5] for this compound.

*cyclo*Hexane*spirocyclo*pentane-2 : 4-dione (V) on treatment with ethyl orthoformate and acetic anhydride in boiling ethyl acetate, followed by hydrolysis, gave 3-formyl*cyclo*hexane-*spirocyclo*pentane-2 : 4-dione (I). This compound gave colours with ferric chloride and with titanous chloride similar to those given by the keto-aldehyde (II; R = Me) with these reagents, and formed a crystalline copper complex and an anil. It is a monobasic acid with p*K* 2·9 in 50% aqueous ethanol.

3-Formyl*cyclo*hexane*spirocyclo*pentane-2 : 4-dione (I) on oxidation with alkaline hydrogen peroxide gave formic acid and 1-carboxy*cyclo*hexylacetic acid (isolated as its anhydride), but on acid hydrolysis gave a high-melting substance of unknown constitution. Similar high-melting products were obtained when solutions of the formyl-diketone were kept for long periods.

*cyclo*Hexane*spirocyclo*pentane-2 : 4-dione (V) was prepared by a modification of Rothstein and Thorpe's synthesis.[8] Ethyl 1-chlorocarbonyl*cyclo*hexylacetate (IV; R = Et, R′ = Cl), on treatment with dimethylcadmium, gave ethyl 1-acetyl*cyclo*hexylacetate (IV; R = Et, R′ = Me) which on hydrolysis to the acid and re-esterification with diazomethane furnished pure methyl 1-acetyl*cyclo*hexylacetate (IV; R = R′ = Me). Cyclisation of this ester by de Rosanbo's method [9] gave the diketone (V).

[4] Vorländer and Guthke, *Ber.*, 1929, **62**, 549.
[5] Meek, Turnbull, and Wilson, *J.*, 1953, 811.
[6] Rogers and Smith, *J.*, 1955, 341.
[7] Weygand and Csendes, *Chem. Ber.*, 1952, **85**, 45.
[8] Rothstein and Thorpe, *J.*, 1926, 2015.
[9] de Rosanbo, *Ann. Chim.* (*France*), 1923, **19**, 327.

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The ultraviolet absorption spectra of 3-formyl*cyclo*pentane*spirocyclo*pentane-2 : 4-dione (I), 2-formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (II; R = Me), and 3-formylpentane-2 : 4-dione have been determined in several solvents (Table 1). Comparison of these results with previous studies of the ultraviolet absorption spectra of 2-acyl-1 : 3-diketones [3,10] shows that, in solvents in which ionisation is suppressed, all these compounds show two bands, in the regions of 240 and 275 mμ respectively, due to the undissociated enols. In the presence of alkali, ionisation is essentially complete and, while the band near 275 mμ suffers little change, the band near 240 mμ is shifted to longer wavelengths. For 2-acyl*cyclo*hexane-1 : 3-diones other than the formyl compounds, and for 3-formylpentane-2 : 4-dione, the two bands due to the anion overlap completely, whereas the anion of compound (II; R = Me) shows a strong band at 260 mμ with an inflexion due to the second band near 275 mμ. Compound (I) provides an extreme case, where the band at 245 mμ is unchanged on passage from the enol to the anion, so that two bands are observed in all solvents. The ultraviolet absorption spectra of compounds (I) and (II; R = Me) were determined in aqueous rubidium hydroxide as well as in sodium hydroxide. Each compound showed virtually identical absorption in the two media, indicating that differential cation effects such as alkali-metal chelation cannot account for the observed differences between the ultraviolet absorption spectra of the anions of these two compounds.

TABLE 1. *Ultraviolet absorption spectra.*

Solvent	$\lambda_{max.}$ (mμ)	ε
3-Formylpentane-2 : 4-dione		
EtOH + 5% of HCl	236, 275	22,190, 19,250
0·1N-NaOH	272	37,140
*2-Formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione* (II; R = Me)		
Acetonitrile	232, 277	10,390, 9,690
0·1N-HCl	235, 272	13,460, 12,930
EtOH	234, 265 i,* 275·5	7,290, 9,930, 10,390
0·1N-NaOH	260, 272 i	17,180, 16,080
0·1N-RbOH	260, 272 i	16,790, 15,690
*3-Formyl*cyclo*hexane*spirocyclo*pentane-2 : 4-dione* (I)		
Acetonitrile	243, 277·5	13,360, 11,330
0·1N-HCl in 20% EtOH	245, 269	15,540, 12,350
EtOH	245, 277·5	16,700, 12,580
0·1N-NaOH	245, 274·5	19,820, 15,440
0·1N-RbOH	245, 274·5	18,930, 14,780

* i denotes an inflexion.

The ultraviolet absorption spectra of compound (II; R = Me) in acetonitrile and in 0·1N-hydrochloric acid are closely similar, indicating that this compound is not appreciably ionised in acetonitrile. In ethanol, however, it must be considerably ionised, since in this solvent there is an inflexion in the region of 265 mμ due to the anion, in addition to the bands due to the enol. These considerations must apply also to the ultraviolet absorption spectrum of 2-formyl*cyclo*hexane-1 : 3-dione (II; R = H), for which Rogers and Smith [6] report maxima at 240 and at 255 mμ (in methanol).

The infrared absorption spectra of these compounds have also been determined (Table 2). No absorption occurs in the region 3500—3100 cm.$^{-1}$ normally associated with the hydroxyl group, but the spiran (I) in the solid state shows weak general absorption in the region 2500—1850 cm.$^{-1}$. Neither 3-formylpentane-2 : 4-dione nor the compound (II; R = Me) has detectable hydroxyl bands in the solid state, but the latter in carbon tetrachloride solution does show general absorption, too broad and weak to measure, on either side of the C–H stretching bands near 2900 cm.$^{-1}$. 3-Formylpentane-2 : 4-dione shows a band at 2840 cm.$^{-1}$ assigned to the formyl group, and may therefore exist partly

[10] Smith, *J.*, 1953, 803.

in the aldehyde form. This band is not observed in the case of compounds (I) or (II; R = Me).

The absence of absorption characteristic of isolated carbonyl groups indicates that all three compounds are completely enolised. In each case, however, the solids show strong bands in the region 1687—1668 cm.$^{-1}$. For compounds (I) and (II; R = Me) in solution, these bands occur at significantly higher frequencies, and are then close to the characteristic frequencies (1715 and 1680 cm.$^{-1}$) of αβ-unsaturated carbonyl groups in five- and in six-membered rings respectively.[11] In addition, compounds (I) and (II; R = Me) show a band in the region 1647—1633 cm.$^{-1}$, attributed to the hydrogen-bonded αβ-unsaturated carbonyl group. This assignment implies the presence of intramolecular hydrogen-bonding in both compounds, since in each case the band is observed in essentially the same position in the solid as in solution. All three compounds show intense bands in the region 1598—1540 cm.$^{-1}$, attributed to conjugate chelation.[3,12] In the case of 3-formylpentane-2 : 4-dione, the broadness and intensity of this absorption probably accounts for the failure to observe a band near 1630 cm.$^{-1}$; likewise compound (II; R = Me) in solution shows a band due to conjugate chelation near 1590 cm.$^{-1}$ while the solid shows intense absorption extending from the maximum at 1633 cm.$^{-1}$ as far as 1550 cm.$^{-1}$.

TABLE 2. *Infrared absorption frequencies* (*cm.*$^{-1}$).

3-Formylpentane-2 : 4-dione	Dione (II; R = Me)		Spiran (I)		
In Nujol	In Nujol	In CCl_4	In Nujol	In $CHCl_3$ + 1% of EtOH	Assignment
2840	—	—	—	—	Formyl CH
—	—	—	2500—1850	—	OH (H-bonded)
1674	1668	1684	1687	1706	C=O (conjugated)
	1633 *	1637	1647	1647	Conjugated chelated system
1540 *		1594 †	1569	1598	

* Very broad, intense bands. † Partly overlapped by solvent absorption.

These findings are consistent with the physical properties of 3-formylpentane-2 : 4-dione and the dione (II; R = Me), which in each case suggest strong intramolecular hydrogen-bonding, but are more difficult to reconcile with the physical properties of the spiran (I). The behaviour of this compound suggests that intramolecular hydrogen-bonding is weaker in this case than in that of the analogue (II; R = Me) or of 3-formylpentane-2 : 4-dione. This effect is probably due to strain in the *cyclo*pentane ring of the spiran, which would result in a larger separation between the formyl and ring-carbonyl groups. A similar effect of ring-strain has been noted for 7-hydroxyphthalide.[13]

2-Formyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (II; R = Me) showed antifungal activity, causing stunting of the germ-tubes of *Botrytis allii* at 6·3 p.p.m., while in this test 3-formyl*cyclo*hexane*spirocyclo*pentane-2 : 4-dione (I) was inactive. Both compounds showed slight antibacterial activity.

EXPERIMENTAL

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Infrared measurements were made with a Grubb-Parsons S 3A single-beam spectrometer through which dry air was continuously circulated. Ultraviolet absorption was determined with a Unicam S.P. 500 Spectrophotometer. p*K* values were determined in water unless otherwise stated.

3-Formylpentane-2 : 4-dione was prepared by Claisen's method,[1] and after recrystallisation from light petroleum (b. p. 40—60°) followed by sublimation at 40—48°/1 mm. had m. p. 40—42° (sealed capillary) (Found: p*K* 4·6). The compound gave a deep orange colour with aqueous ferric chloride, a wine-red colour with titanous chloride[7] in methanol (blue in the

[11] Grove and Willis, *J.*, 1951, 877.

[12] Cf. Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068; Bellamy and Beecher, *J.*, 1954, 4487.

[13] Duncanson, Grove, and Zealley, *J.*, 1953, 1331.

presence of pyridine), and a violet lower phase when shaken with chloroform and aqueous cupric acetate. The copper complex was obtained as purple crusts, m. p. 215—216° from ethanol, or as deep blue prisms, m. p. 213—214° from chloroform–carbon tetrachloride.

2-Formyl-5 : 5-dimethylcyclohexane-1 : 3-dione.—5 : 5-Dimethylcyclohexane-1 : 3-dione (dimedone) (2·50 g.), ethyl orthoformate (7·5 g.), and acetic anhydride (10·8 g.) were heated under reflux for 45 min. Evaporation of the product under reduced pressure gave a dark residue which was treated with 3N-sodium hydroxide (15 ml.). The alkaline mixture was washed with ether (50 ml.), and the ether washings were shaken with 3N-sodium hydroxide (8 × 10 ml.). The combined alkaline extracts on acidification with concentrated hydrochloric acid, extraction with ether (4 × 50 ml.), and evaporation of the dried ethereal extracts, gave a crystalline residue which was sublimed twice at 100°/20 mm., to give *2-formyl-5 : 5-dimethylcyclohexane-1 : 3-dione* as prisms, m. p. 74—76·5° (0·52 g.). Recrystallisation from light petroleum (b. p. 60—80°) followed by sublimation at 75°/16 mm. raised the m. p. to 76—77° [Found: C, 64·0; H, 7·5%; equiv., 167; *M* (Rast), 233. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%; *M*, 168]. The compound liberated carbon dioxide from sodium carbonate solution.

The *copper complex*, prepared by the addition of 2-formyl-5 : 5-dimethylcyclohexane-1 : 3-dione to a solution of cupric acetate monohydrate in methanol and evaporation of the mixture under reduced pressure, formed blue leaflets, m. p. 310—310·5° (decomp.), from chloroform–ethanol (Found: C, 54·3; H, 5·7; Cu, 15·2. $C_{18}H_{22}O_6Cu$ requires C, 54·3; H, 5·6; Cu, 16·0%). The *anil* prepared in the usual manner formed leaflets, m. p. 136·5—137·5°, from light petroleum (b. p. 60—80°) (Found: C, 74·0; H, 7·3; N, 6·2. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%), $\lambda_{max.}$ 234, 255, 349 mμ (ε 9600, 10,350, 27,070) in EtOH. Infrared absorption bands were: (i) in Nujol, 1675 and 1595 (broad) cm.$^{-1}$; (ii) in CCl_4, 1675, 1610, 1598, and 1574 cm.$^{-1}$.

The ethereal solution remaining after the extraction with aqueous sodium hydroxide was washed with 25% sodium chloride solution, dried, and evaporated. A solution of the residue in ethanol (20 ml.) was treated with 3N-sodium hydroxide (10 ml.), and the ethanol removed at 25° under reduced pressure. The sodium salt which separated was collected, washed with ether, and an aqueous solution acidified, giving 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-9-(2-hydroxy-4 : 4-dimethyl-6-oxocyclohex-1-enyl)-3 : 3 : 6 : 6-tetramethyl-1 : 8-dioxoxanthen (III), m. p. 223—226° (0·45 g.). Recrystallisation from methanol furnished needles, m. p. 227—228° (decomp.) alone or mixed with a specimen prepared according to Vorländer and Guthke's method [4] [Found: C, 73·0, 72·6; H, 8·0, 7·9%; *M* (Rast), 471; equiv., 353; p*K* 8·0 (in 50% aqueous ethanol). Calc. for $C_{25}H_{32}O_5$: C, 72·8; H, 7·8%; *M*, 412·5], $\lambda_{max.}$ 236 mμ (ε 22,210) in EtOH. The two samples had identical infrared absorption spectra in Nujol (bands at 3240, 1654, 1619, and 1587 cm.$^{-1}$). The compound gave no colour with ferric chloride in aqueous methanol.

Oxidation of 2-Formyl-5 : 5-dimethylcyclohexane-1 : 3-dione.—A solution of the formyl-diketone (78 mg.) in 0·2N-sodium hydroxide (25 ml.) and 6% hydrogen peroxide (6 ml.) was set aside at room temperature. After 3 days further 6% hydrogen peroxide (4 ml.) was added, and after 6 days the solution was acidified with 3N-sulphuric acid (3 ml.) and distilled to small bulk (10 ml.). The distillate was neutralised with 0·1N-barium hydroxide (5 ml.), saturated with carbon dioxide, boiled for 5 min., and filtered hot. Evaporation of the filtrate gave a white residue (26 mg.), giving a strong positive reaction for formate in the chromotropic acid test.[14] The residue from the distillation, on continuous extraction with ether (20 hr.) and evaporation of the dried ethereal extract, gave crystals, m. p. 95—97·5° (72 mg.), which on recrystallisation from benzene gave colourless plates (63 mg.), m. p. 98—99·5° alone or mixed with ββ-dimethylglutaric acid.

Acid Hydrolysis of 2-Formyl-5 : 5-dimethylcyclohexane-1 : 3-dione.—The formyl-diketone (11·5 mg.) in N-sulphuric acid (2 ml.) was heated for 4 hr. at 120° under reflux in a current of nitrogen. The mixture was then cooled and the crystalline product collected (4·8 mg.); it had m. p. 225—226·5° alone or mixed with the xanthen (III).

Condensation of 2-Formyl-5 : 5-dimethylcyclohexane-1 : 3-dione with Dimedone.—The formyl-diketone (30 mg.) and dimedone (50 mg., 2 mols.) in ethanol (5 ml.) were heated under reflux for 1·5 hr., and the mixture concentrated and cooled. The pinkish needles which appeared were collected and washed with ethanol. Evaporation of the filtrate and treatment of the residue with ether gave further material which was washed with ether and combined with the remainder of the product, giving in all 67 mg. (91%) of the condensation product, m. p. 224—227°, alone or mixed with the xanthen (III).

[14] **Feigl**, "Spot Tests," 4th edn., Vol. II, p. 245, Elsevier, Amsterdam.

1-*Acetyl*cyclo*hexylacetic acid*. Ethyl 1-carboxy*cyclo*hexylacetate [8, 15] (41·4 g.) was heated with thionyl chloride (33 g.) until evolution of hydrogen chloride ceased. Removal of the excess of thionyl chloride under reduced pressure yielded crude ethyl 1-chlorocarbonyl*cyclo*hexylacetate.

A solution of methylmagnesium bromide (from 9·4 g. of magnesium and an excess of methyl bromide in 200 ml. of dry ether) at 0° was treated with anhydrous cadmium chloride (37·6 g.), then stirred until it gave a negative Gilman reaction [16] for Grignard reagent (15 min.). After removal of most of the ether, dry benzene (130 ml.) was added, and further solvent (50 ml.) distilled off. Further benzene (240 ml.) was then added and the mixture heated to the b. p. A solution of the foregoing acid chloride in benzene (60 ml.) was next added as rapidly as possible to the hot dimethylcadmium solution. After the vigorous reaction had subsided, the mixture was heated under reflux for 10 min., and, after a further 10 min., cooled and treated cautiously with ice and 3N-sulphuric acid. The benzene layer was separated, washed with 5% sodium carbonate solution and with saturated sodium chloride solution, dried, and evaporated. The oily product (35·9 g.) was heated under reflux with 50% (w/v) potassium hydroxide (36 ml.) and ethanol (72 ml.) for 2 hr. After removal of the ethanol under reduced pressure the solution was acidified and extracted with ether. Evaporation of the ethereal extract gave an orange oil (30·6 g.) which was distilled under reduced pressure. The distillate (27·2 g.; b. p. 155—175°/13 mm.) was dissolved in ether (150 ml.) and extracted with saturated sodium hydrogen carbonate solution (6 × 40 ml.), and the combined aqueous extracts were washed with ether (50 ml.) and acidified. Extraction of the product with ether (4 × 75 ml.) and evaporation of the extracts gave an oil (23·0 g., 65%) which crystallised. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure keto-acid, m. p. 78—80° (18 g., 50%).

cyclo*Hexane*spirocyclo*pentane*-2 : 4-*dione*.—Sodium methoxide (from 2·43 g. of sodium) was powdered and suspended in dry ether (30 ml.). Methyl 1-acetyl*cyclo*hexylacetate (20·9 g.; b. p. 131—132°/11 mm.; n_D^{20} 1·4695; prepared in 99% yield from the above acid) was added and the mixture shaken for 48 hr. at room temperature. Ice and an excess of 3N-sulphuric acid were then added, and the solid which separated was collected (5·0 g.; m. p. 179—180°). Evaporation of the ether layer gave further material (1·1 g.). Recrystallisation of the combined products from aqueous ethanol gave transparent prisms, m. p. 180° (5·4 g., 30%) (Found: C, 71·9; H, 8·5. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·5%). Ultraviolet absorption spectrum: (i) in EtOH containing 5% of 10N-HCl, $\lambda_{max.}$ 243 mμ (ε 15,190); (ii) in 0·1N-NaOH, $\lambda_{max.}$ 260 mμ (ε 27,700). Infrared absorption bands (in $CHCl_3$) at 1728 and 1668 cm.$^{-1}$.

3-*Formyl*cyclo*hexane*spirocyclo*pentane*-2 : 4-*dione*. — *cyclo*Hexane*spirocyclo*pentane-2 : 4-dione (1·066 g.), ethyl orthoformate (4·7 g.), acetic anhydride (7·0 g.), and dry ethyl acetate (40 ml.) were heated under reflux for 6 hr. and the mixture evaporated under reduced pressure. The partly crystalline residue on sublimation at 100—130°/0·5 mm. gave a yellow solid (0·725 g.) which was dissolved in 0·5N-sodium hydroxide at 0°. The cold solution when filtered and made just acid with 3N-hydrochloric acid at 0° gave the *formyl-diketone* which separated as cream-coloured leaflets, m. p. 151—155·5° (0·492 g., 40%). Recrystallisation from methanol–ether at <0° raised the m. p. to 159—160·5° [Found: C, 68·2; H, 7·4%; equiv., 196. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%; equiv. (monobasic), 194].

The compound gave an intense orange colour with ferric chloride, a violet colour with titanous chloride in methanol, and a transient deep green colour with the latter reagent in the presence of pyridine. It was readily soluble in most organic solvents, except ether and light petroleum. It was sparingly soluble in water but dissolved readily in dilute aqueous sodium hydroxide, and decomposed slowly in the presence of water or of mineral acids, giving a brown crystalline solid, m. p. 185—195°, of unknown constitution.

The *copper complex* prepared as above formed turquoise-blue prisms, m. p. 300—304° (decomp.), from chloroform–methanol (Found: C, 58·0; H, 6·0; Cu, 13·8. $C_{22}H_{26}O_6Cu$ requires C, 58·7; H, 5·8; Cu, 14·1%). The *anil* formed needles, m. p. 133·5°, from chloroform–light petroleum (b. p. 60—80°) (Found: C, 76·0; H, 7·1; N, 5·5. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%), $\lambda_{max.}$ 237, 350 (sh), 353 mμ (ε 15,600, 26,060, 26,260), in EtOH. Infrared absorption bands: (i) in Nujol, 3200, 1700, 1634, and 1589 cm.$^{-1}$; (ii) in CCl_4, 1703, 1630, and 1585 cm.$^{-1}$.

Oxidation of 3-*Formyl*cyclo*hexane*spirocyclo*pentane*-2 : 4-*dione*.—The formyl-diketone (76

[15] Cf. Harding, Haworth, and Perkin, *J.*, 1908, **93**, 1958; Lapworth and McRae, *J.*, 1922, **121**, 2754.
[16] Gilman and Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

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mg.) on oxidation with alkaline hydrogen peroxide by the method described above gave a volatile acid fraction of which the barium salt (10 mg.) gave a positive reaction for formate.[14] The non-volatile oxidation products on continuous extraction with ether and evaporation of the extracts yielded a solid, m. p. 95—115° (69 mg.), which sublimed at 160—200°/20 mm. The oily sublimate was dried over potassium hydroxide and extracted with light petroleum (b. p. 40—60°). The concentrated extracts when cooled to −60° deposited colourless leaflets m. p. 49—53° (22 mg.). Further recrystallisation from the same solvent raised the m. p. to 53—54°, raised to 53·5—55° on admixture with the anhydride of 1-carboxy*cyclo*hexylacetic acid.

Acid Hydrolysis of 3-*Formyl*cyclo*hexane*spirocyclo*pentane*-2 : 4-*dione*.—The formyl-diketone (8·2 mg.) was heated with N-sulphuric acid (2 ml.) at 120° under reflux in a current of nitrogen for 4 hr. The mixture when cooled deposited a yellow substance, m. p. 193—196·5° (4·6 mg.), which could not be further characterised.

We are indebted to Dr. L. A. Duncanson for determining the infrared absorption spectra, to Mr. H. G. Hemming for the biological assays, and to several colleagues for suggestions and criticisms.

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968. *Complex Fluorides. Part XI.* The Preparation and Infrared Spectra of Tri-*p*-tolylaminium Salts.*

By D. W. A. Sharp.

Tri-*p*-tolylaminium salts, $(C_7H_7)_3N^{\cdot+}$, of complex fluoro-acids can be prepared by oxidation of tri-*p*-tolylamine with a mixture of iodine and the silver salt of the complex fluoro-acid. The deep blue free-radical aminium salts are fairly stable to hydrolysis. The infrared spectra of tri-*p*-tolylaminium salts of both complex fluoro-acids and perchloric acid show no sign of covalent bonding between the cation and the anion. The spectrum of the tri-*p*-tolylaminium cation has been compared with the spectra of the triphenylmethyl carbonium ion and the tri-*p*-tolylmethyl carbonium ion and favours the crystalline aminium salts' having a D_3, propeller-like, configuration.

Sidgwick [1] lists two main types of aryl-nitrogen free radicals, the type depending upon the arrangement of valency electrons. Free radicals of nitrogen arise either by homolytic fission of an N–N bond or by oxidation, involving the removal of one electron, of the lone-pair in a nitrogen compound. The formation of the diaryl-nitrogen compound by dissociation of the tetra-arylhydrazines [2] is an example of the first type of reaction, and the oxidation of tri-*p*-tolylamine to the tri-*p*-tolylaminium cation of the second.

The nature of the aminium salts, first prepared by Wieland,[3] was elucidated by Weitz and Schwechten,[4] who showed that the deep blue products of the action of oxidising agents upon tri-*p*-tolylamine were salts of the tri-*p*-tolylaminium cation, $(CH_3{\cdot}C_6H_4)_3N^{\cdot+}$. In particular, it was shown that tri-*p*-tolylamine reacts with the solution resulting from the action of iodine upon silver perchlorate in ether to give tri-*p*-tolylaminium perchlorate. This solution was supposed to contain the chlorine tetroxide radical, but subsequent work [5] showed that the solution contains iodine perchlorate, the solvated iodine cation

* Part X, *J.*, 1957, 4132.

[1] Sidgwick, "The Chemical Elements and their Compounds," Oxford Univ. Press, 1950.
[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1500.
[3] Wieland, *Ber.*, 1907, **40**, 4263.
[4] Weitz, *Angew. Chem.*, 1922, **39**, 1193; Weitz and Schwechten, *Ber.*, 1926, **59**, 2307; 1927, **60**, 545.
[5] Hazeldine and Sharpe, *J.*, 1952, 993.

being an extremely powerful oxidising and iodinating agent. Sharpe [6] demonstrated that silver fluoroborate and iodine in ether gave a very similar solution containing iodine fluoroborate [7] and we have now shown that solvated iodine cations are formed by many silver salts of complex fluoro-acids, since the iodine cation, in each case, will oxidise tri-*p*-tolylamine to the tri-*p*-tolylaminium cation. Ethereal solutions containing positive iodine are extremely unstable; in the absence of tri-*p*-tolylamine the solvent is immediately iodinated.[5] Since the reaction proceeds by way of this oxidation the failure of triphenylamine to give similar aminium salts is understandable. Oxidation of triphenylamine may momentarily produce the appropriate free radical but there is immediate intermolecular attack through the highly activated *para*-positions with formation of tetraphenylbenzidine.[7] The stability of tri-*p*-tolylaminium salts to attack at the *para*-position is further enhanced by their great insolubility in ether and their removal from the possibility of further reaction.

Using the above reaction we prepared tri-*p*-tolylaminium fluoroborate, hexafluorophosphate, hexafluoroarsenate, hexafluoroniobate, hexafluorotantalate, and fluorosulphate. In addition, the hexafluoroantimonate was prepared and characterised by its infrared spectrum. This salt does not give consistent analytical results and it seems probable that antimony pentafluoride, which is presumably evolved on ignition, prevents complete combustion to carbon dioxide. Salts of complex fluoro-acids are often extremely difficult to analyse because of such interference.

We tried to prepare tri-*p*-tolylaminium trifluoroacetate since Haszeldine and Sharpe [5] have shown that iodine and silver trifluoroacetate react in ether to give a solution which contains a strong iodinating agent, presumably the solvated iodine cation, but were unsuccessful; addition of silver trifluoroacetate to a solution containing tri-*p*-tolylamine and iodine gave the deep blue colour characteristic of the aminium salts, but this rapidly faded to give a brown sludge of unknown composition. There are two possible causes of this decomposition: the tri-*p*-tolylaminium trifluoroacetate could be soluble in ether and thus react further with the active products present, or, by analogy with triphenylmethyl trifluoroacetate the aminium trifluoroacetate being formed might be expected to have predominantly covalent character; [8] the resulting nine valency electrons about the central nitrogen atom would cause great instability.

The infrared spectra of tri-*p*-tolylaminium perchlorate, chloroantimonate, and perbromide were described by Otting and Kainer,[9] who detected differences between their spectra and concluded that only in the perchlorate was the bonding purely ionic. Such covalent bonding cannot occur [10] in the salts of many complex fluoro-acids, whose infrared spectra should thus be those of the complex fluoro-anions superimposed on the spectra of the cations. Accordingly, the spectra of tri-*p*-tolylaminium salts of complex fluoro-acids showed a constant background due to the cation and the peaks corresponding to absorption by the anions occurred at positions expected for the completely free anions. The cation spectra now recorded are closely similar to Otting and Kainer's for tri-*p*-tolylaminium chloroantimonate but differ from their spectrum of the perchlorate. A repetition of the infrared spectrum of tri-*p*-tolylaminium perchlorate showed that, in fact, the spectrum of the aminium cation in this substance is identical with that obtained for the tri-*p*-tolylaminium cations in salts of complex fluoro-acids. The spectrum also contains rather diffuse bands which are characteristic of the perchlorate ion. We conclude that in no tri-*p*-tolylaminium salt so far examined is there evidence for anion–cation interaction. In Otting and Kainer's work there was possibly some decomposition in the potassium bromide disc and it may be significant that their spectrum of tri-*p*-tolylaminium perchlorate is fairly closely similar to that of tri-*p*-tolylamine, thus indicating possible decomposition to the latter.

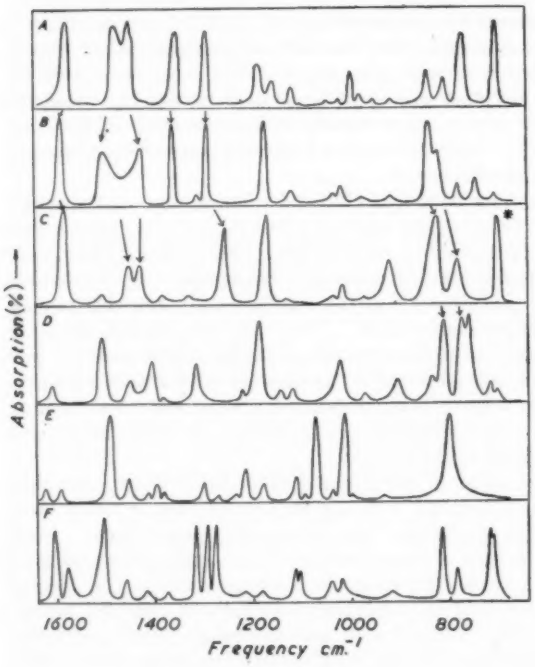
[6] Sharpe, *J.*, 1952, 4538.
[7] Wieland, *Ber.*, 1913, **46**, 3301; Madelung, Reiss, and Herr, *Annalen*, 1927, **454**, 36.
[8] Sharp and Sheppard, *J.*, 1957, 674.
[9] Otting and Kainer, *Chem. Ber.*, 1954, **87**, 1205.
[10] Sharp and Sharpe, *J.*, 1956, 1855, 1858.

The infrared peaks characteristic of the anions now studied ($cm.^{-1}$) were as follows, with figures for potassium salts (except for AsF_6, rubidium salt) for comparison:

Anion =	BF_4	PF_6	AsF_6	SO_3F	ClO_4
$(C_7H_7)_3N^+$	1075 (diffuse)	845 s	698 s	710 m, 1065 s, 1283 s	1092 s, 1122 m
K or Rb	1032, 1058 [11]	845 [12]	700 [10]	732 s, 1073 s, 1277 s [13]	1075 s, 1122 s [14]

*The Infrared Spectrum and Structure of the Tri-*p*-tolylaminium Ion.*—The Figure shows infrared spectra of three ions and three reference compounds in the region likely to show absorption sensitive to the configuration of the cation. Except for tri-*p*-tolylaminium hexafluoroarsenate the anions do not absorb in this region.

The problem of the structure of the tri-*p*-tolylaminium ion is similar to that of the



A, $Ph_3C^+SnCl_5^-$; *B*, $(p\text{-}C_7H_7)_3C^+NbF_6^-$; *C*, $(p\text{-}C_7H_7)_2N^+AsF_6^-$; *D*, $(p\text{-}C_7H_7)_3CCl$; *E*, $p\text{-}C_7H_7Br$; *F*, $(p\text{-}C_7H_7)_3N$.

* Absorption due to the AsF_6^- ion.

triphenylmethyl carbonium ion, the difference in the electronic structures of the tri-*p*-tolylmethyl carbonium ion and the tri-*p*-tolylaminium ion being the presence of one extra electron in the latter. The identity of tri-*p*-tolylaminium perchlorate as a free radical has been established from the paramagnetic susceptibility.[15] Thus the tri-*p*-tolylaminium ion is isoelectronic with the tri-*p*-tolylmethyl radical and hence a knowledge of the structure of the aminium ion will be very strong evidence for the structure of the carbon free radicals.

The triphenylmethyl carbonium ion is, from its infrared spectrum, probably planar, propeller-like in structure.[8] Many factors, particularly those relating to the steric effects of bulky aromatic rings, which influence the structure of carbonium ions are also important in the structure of the aminium salts. However, the configuration about the central

[11] Coté and Thompson, *Proc. Roy. Soc.*, 1951, *A*, **210**, 217.
[12] de Lattre, *J. Chem. Phys.*, 1951, **19**, 1610.
[13] Sharp, *J.*, 1957, 3761.
[14] Miller and Wilkins, *Analyt. Chem.*, 1952, **24**, 1253.
[15] Rumpf and Trombe, *Compt. rend.*, 1938, **206**, 671.

nitrogen atom may be influenced by the extra electron in the latter ion. From molecular-orbital theory, Walsh concludes that the methyl radical should be pyramidal [16] but, from spectra, Herzberg and Shoosmith conclude that it is only slightly bent in its ground state and planar in an upper state.[17] For the aminium ion or for the triphenylmethyl free radical, resonance stabilisation will be a maximum for an all-planar configuration of the ion.[18,19,20] Swarc has pointed out that steric effects between the *ortho*-hydrogen atoms would make a completely planar structure impossible for the triphenylmethyl free radical [21] but the strain could be relieved by rotation of one or more aromatic rings about the central bonds. As for the triphenylmethyl cation, this rotation would not necessarily inhibit conjugation between the separate rings as the valency bonds to the central carbon atom would remain coplanar.

Little evidence exists for the structure of the tri-*p*-tolylaminium cation. Otting and Kainer [9] discussed its infrared spectrum in terms of an all-planar structure of symmetry D_{3h}, basing their evidence on Karagounis's [22] work on the triphenylmethyl radical which was also considered to have symmetry D_{3h}. However, the latter work is based on doubtful assumptions [8] and Otting and Kainer's discussion must be reconsidered. For the structures of the isoelectronic carbon free radicals there is more evidence, although it is not very definite. Chu and Weissman [23] have discussed the absorption and luminescent spectra of the triphenylmethyl free radical in terms of a structure of symmetry C_3 and consider that paramagnetic resonance supports this conclusion.[24] However, studies of the stabilisation of the triphenylmethyl radical in solid solutions of planar molecules such as fluorene suggest that the radical itself is planar.[25] Brown and Dodson [26] suggest that the entry of an electron into trimesitylboron, to form the trimesitylboron anion free radical, is into a non-localised orbital. The most readily envisaged stereochemical form of such a free radical, isoelectronic with the aminium salts and the carbon free radicals, is planar about the central boron atom.

For an entity as complicated as the tri-*p*-tolylaminium ion we cannot completely assign all the observed infrared bands to decide definitely the symmetry of the ion. Such a decision can be made only by comparing the infrared spectrum with those of compounds of known structure. From comparison with the spectrum of triphenylboron, the triphenylmethyl carbonium ion probably has a planar arrangement of the bonds about the central atom.[8] The infrared spectra of the triphenylmethyl carbonium ion, the tri-*p*-tolylmethyl carbonium ion, and the tri-*p*-tolylaminium ion show well-marked resemblance, between each other, but are completely distinct from those of compounds such as chlorotri-*p*-tolylmethane where a planar structure is not possible. These resemblances are particularly well marked in the spectra of the three cations near 1580, 1480, 1445, and 1300 cm.$^{-1}$, the bands being much stronger than those of *p*-bromotoluene and chlorotri-*p*-tolylmethane. For triphenylmethyl and tri-*p*-tolylmethyl salts there is a strong band near 1360 cm.$^{-1}$, but this is weak for tri-*p*-tolylaminium salts; however, it is also very weak in the spectrum of triphenylboron [8] and must be very sensitive to changes in substituents. These bands are all associated with skeletal stretching vibrations of the aromatic rings [27] and the enhanced intensity of this type of vibration is due to the greater dipole changes over the conjugated system than those over the aromatic systems of the

[16] Walsh, *J.*, 1953, 2296.
[17] Herzberg and Shoosmith, *Canad. J. Phys.*, 1956, **34**, 523.
[18] Pauling and Wheland, *J. Chem. Phys.*, 1933, **1**, 362.
[19] Hückel, *Z. Physik*, 1933, **83**, 632.
[20] Dewar, *Proc. Cambridge Phil. Soc.*, 1949, **45**, 638.
[21] Swarc, *Discuss. Faraday Soc.*, 1947, No. 2, 42.
[22] Karagounis, *Helv. Chim. Acta*, 1951, **34**, 994.
[23] Chu and Weissman, *J. Chem. Phys.*, 1954, **22**, 21.
[24] Weissman and Sowden, *J. Amer. Chem. Soc.*, 1953, **75**, 503, and personal communication.
[25] Aston, Fritz, and Seki, *J. Amer. Chem. Soc.*, 1957, **79**, 1000.
[26] Brown and Dodson, *ibid.*, p. 2302.
[27] Randle and Whiffen, "Molecular Spectroscopy," Institute of Petroleum, London, 1955, p. 111; Whiffen, *J.*, 1956, 1350.

simpler derivatives. The constancy of the pattern shows that all the ions have similar, presumably planar, arrangements about their central atoms. Tri-*p*-tolylamine also has a very strong band at about 1600 cm.$^{-1}$; this is not the same band that is enhanced in intensity at 1580 cm^{-1} in the carbonium and aminium salts, the latter band also occurring at about 1580 cm^{-1} in tri-*p*-tolylamine but being only of medium intensity.

The resemblance between the spectra of the three cations is continued over the range 1300—900 cm.$^{-1}$. The enhanced intensity of the δ_3 vibration at about 1180 cm.$^{-1}$ [28] is not especially characteristic of the spectra of planar radical ions as has been claimed by Otting and Kainer,[9] since this band is also very strong in chlorotri-*p*-tolylmethane.

Apart from the extra band at about 1360 cm.$^{-1}$ in the spectra of triphenylmethyl and tri-*p*-tolylmethyl salts the only major differences between the spectra of the three cations come in the region 900—700 cm.$^{-1}$, this being the region most sensitive to ring substitution. Spectra of tri-*p*-tolylmethyl salts and tri-*p*-tolylaminium salts remain fairly similar, except that one additional peak of medium intensity occurs near 900 cm.$^{-1}$ in that of the aminium salt. The strong band near 800 cm.$^{-1}$ in *para*-substituted benzenes corresponds to the C–H out-of-plane vibration. In *p*-bromotoluene this vibration belongs to the symmetry class B_2 and hence, in accordance with the selection rules given for the triphenylmethyl carbonium ion,[8] should split into three components in a unsymmetrical planar structure, two in a D_3 propeller-like structure, and remain as one in a planar D_{3h} structure. This band is clearly split into two components in the spectra of both tri-*p*-tolylmethyl carbonium salts and tri-*p*-tolylaminium salts and, although not giving a completely definite decision since one component may possibly not be resolved, this splitting favours a planar, propeller-like structure for both these salts. The spectrum of chlorotri-*p*-tolylmethane also shows a similar splitting and, in this case, the lower band appears further split into a close-lying doublet. This subsidiary splitting does not occur in the spectra of fluorotri-*p*-tolylmethane or tri-*p*-tolylmethanol and, although it may be due to the symmetry of the molecule in chlorotri-*p*-tolylmethane, it is more likely due to intermolecular interactions or split degeneracy, the molecule being on a site of lower symmetry than itself.[8]

The mean values of the C–H out-of-plane frequencies of the tri-*p*-tolylmethyl carbonium ion and the tri-*p*-tolylaminium ion are 834 and 804 cm.$^{-1}$ respectively. Electrophilic substituents markedly increase the frequencies of this type of vibration [30,31] and the value for the tri-*p*-tolylmethyl cation shows the effect of the interaction of the π-electron system of the aromatic rings with the formally vacant *p* orbital of the central carbon atom. The spectrum of the tri-*p*-tolylaminium ion does not show such a shift and the orbital containing the one unpaired electron cannot have a pronounced electron-withdrawing effect on the aromatic system.

Experimental

Silver salts of complex fluoro-acids were prepared with bromine trifluoride as described previously.[10] Silver perchlorate was prepared by the action of excess of silver carbonate on aqueous perchloric acid. The solution was evaporated to dryness and the last traces of water removed at 130° (Found: Ag, 51·6. Calc. for $AgClO_4$: Ag, 51·9%).

Tri-*p*-tolylamine was prepared by standard methods; *p*-toluidine and its hydrochloride were heated to produce di-*p*-tolylamine,[32] which was converted with *p*-iodotoluene into tri-*p*-tolylamine. Recrystallised from glacial acetic acid,[32] it had m. p. 117° (Wieland [33] records 117°).

For the preparation of *tri-*p*-tolylaminium salts*, tri-*p*-tolylamine was dissolved in anhydrous ether and a solution of iodine in ether added. On addition of the silver salt dissolved in ether, silver iodide and the deep blue aminium salt were precipitated. The aminium salt was extracted with the minimum quantity of chloroform and the solvent removed in a stream of dry air.

[28] Kohlrausch and Paulsen, *Monatsh.*, 1939, **72**, 268.
[29] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954.
[30] *Idem*, *J.*, 1955, 2818.
[31] Kross, Fassel, and Margoshes, *J. Amer. Chem. Soc.*, 1956, **78**, 1332.
[32] Rumpf, *Bull. Soc. chim. France*, 1940, **7**, 643.
[33] Wieland, *Ber.*, 1907, **40**, 4260.

The salts are slowly hydrolysed by atmospheric moisture but, with fast work, can be handled in the open. They are stable for months in a sealed tube. Owing to their intense colour, m. p.s could not be determined exactly [Found: C, 67·6; H, 5·9. $C_{21}H_{21}N,BF_4$ requires C, 67·4; H, 5·6. Found: C, 57·8; H, 4·9. $C_{21}H_{21}N,PF_6$ requires C, 58·3; H, 4·85. Found: C, 52·5; H, 4·6. $C_{21}H_{21}N,AsF_6$ requires C, 53·0; H, 4·4. Found: C, 50·8; H, 4·7. $C_{21}H_{21}N,NbF_6$ requires C, 51·1; H, 4·3. Found: C, 42·3; H, 3·6; Ta, 30·8. $C_{21}H_{21}N,TaF_6$ requires C, 43·3; H, 3·6; Ta, 31·3 (Ta was determined as Ta_2O_5 after ignition of the aminium salt). Found: C, 65·5; H, 5·6. $C_{21}H_{21}N,SO_3F$ requires C, 65·3; H, 5·4. Found: C, 65·4; H, 5·3. Calc. for $C_{21}H_{21}N,ClO_4$: C, 65·2; H, 5·5%]. The hexafluoroantimonate, prepared similarly, had the infrared spectrum expected for an aminium salt but could not be consistently analysed.

Chlorotri-*p*-tolylmethane was prepared from the carbinol (m. p. 94°) [prepared according to Mothwurf [34] from *p*-tolylmagnesium iodide and methyl *p*-toluate (Mothwurf records m. p. 96·5°)] which was converted by distillation with acetyl chloride [35] and recrystallising from light petroleum (b. p. 60—80°) into the chloro-derivative, m. p. 178° (Hey *et al.*[35] give m. p. 180°). Tri-*p*-tolylmethyl *salts* were prepared and characterised similarly to triphenylmethyl salts [8] (all equivs. as AgCl precipitated per equiv. of chlorotri-*p*-tolylmethane. Found: for the fluoroborate 1·01, hexafluorophosphate 0·99, hexafluoroniobate 0·99). They are yellow, crystalline solids, similar in every respect to triphenylmethyl carbonium salts. Their infrared spectra are that of the complex fluoro-anion superimposed on the background spectrum of the tri-*p*-tolylmethyl carbonium ion, the latter being the same for all the salts.

*Fluorotri-*p*-tolylmethane* was prepared similarly to fluorotriphenylmethane [36] by adding excess of anhydrous hydrogen fluoride to chlorotri-*p*-tolylmethane, allowing the excess to evaporate, and recrystallising the product from light petroleum. It had m. p. 115° (Found: C, 86·7; H, 6·8. $C_{22}H_{21}F$ requires C, 86·9; H, 6·9%).

Infrared spectra were measured in suspension in Nujol and hexachlorobutadiene mulls on a Perkin-Elmer Model 21 spectrometer with rock-salt optics. Mulls of tri-*p*-tolylmethyl carbonium salts were prepared and kept in the "dry box."

Detailed infrared spectra (cm.$^{-1}$) are given below. These figures are representative of those obtained with salts containing the tri-*p*-tolylmethyl carbonium and tri-*p*-tolylaminium ions, all the other salts studied and containing the same cation giving almost identical spectra.

$Ph_3C^+SnCl_5^-$: 646w, 702s, 770m, 807m, 842m, 915w, 955w,sh, 980w, 997m, 1025w, 1046w, 1100w, 1166w, 1185m, 1293s, 1355s, 1406w,sh, 1448s, 1480s, 1577s, 1649m*, 2920w, 3040w, 3330m*.

$(p\text{-}C_7H_7)_3C^+NbF_6^-$: 710w, 746m, 780m, 823m, 839s, 919w, 975w, 1017m, 1030w, 1120w, 1185s, 1294s, 1314w, 1362s, 1427s, 1503s, 1595s, 2590w, 2860m, 2930m, 2970m.

$(p\text{-}C_7H_7)_3N^+AsF_6^-$: 700s†, 782m, 827s, 920m, 1019m, 1037w, 1127w, 1177s, 1257s, 1327w, 1385w, 1428s, 1454s, 1507w, 1582s, 1645w, 1920w, 2920m, 3060w.

$(p\text{-}C_7H_7)_3N^+ClO_4^-$: 700w, 777m, 822s, 915m, 1017w,sh, 1040w, 1092s, 1122w, 1169s, 1262s, 1320m, 1382w, 1429m, 1452m, 1505w, 1581s, 1642w, 2920w, 3050m, 3200w.

$(p\text{-}C_7H_7)_3N^+SbF_6^-$: 660s, 704m, 781s, 826s, 920m, 970w, 1017m, 1034m, 1128w, 1175s, 1220w, 1256s, 1328w, 1430m, 1450m, 1508w, 1583s, 1641w, 1925w, 1383w, 2610w, 2745w, 2870w, 2940m, 3080w.

$(p\text{-}C_7H_7)_3CCl$: 676w, 704w, 715w, 768s, 776s, 811s, 833m, 904m, 969w, 1018s, 1115w, 1144w, 1185s, 1204w, 1312m, 1380w, 1405m, 1450w, 1506s, 1608w, 1940w, 2860m, 2900s, 3020s.

$p\text{-}C_7H_7Br$: 799s, 932w, 955w, 1013s, 1037w, 1071s, 1092w, 1112m, 1178w, 1212m, 1231w, 1270w, 1300w, 1381w, 1396w, 1411w, 1452m, 1490s, 1592w, 1621m, 1774w, 1887m, 2920m, 3020w.

$(p\text{-}C_7H_7)_3N$: 640w, 714m, 781w, 815s, 920w, 1038w, 1113m, 1175w, 1216w, 1280s, 1297s, 1324s, 1380w, 1424w, 1457w, 1510s, 1585w, 1619m, 2900m, 2960m, 3060m.

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* These peaks are attributed to traces of moisture.
† Absorption due to AsF_6^- ion.

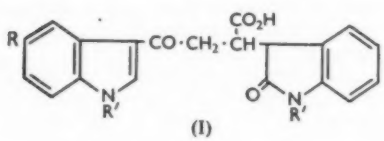
[34] Mothwurf, *Ber.*, 1904, **37**, 3155.
[35] Davies, Hey, and Williams, *J.*, 1956, 4401.
[36] Blicke, *J. Amer. Chem. Soc.*, 1924, **46**, 1515.

969. *The Chemistry of Bacteria. Part VI.* The Synthesis of a Trimethyl Derivative of the C_{20} Acid from Violacein.*

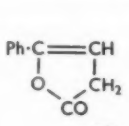
By C. B. Barrett, R. J. S. Beer, G. M. Dodd, and Alexander Robertson.

The synthesis of γ-(5-methoxy-1-methyl-3-indolyl)-α-(1-methyl-3-oxindolyl)-γ-oxobutyric acid (I; R = OMe, R′ = Me) has confirmed the structure (I; R = OH, R′ = H) assigned to the C_{20} acid [1] obtained by degradation of violacein.

The structure (I; R = OH; R′ = H) which was assigned to the C_{20} acid [1] obtained from violacein by treatment with alkali in the presence of zinc has now been confirmed by the synthesis of the trimethyl derivative (I; R = OMe, R′ = Me). In exploratory experiments it was found that the lactone (II), prepared by dehydration of β-benzoylpropionic acid with acetic anhydride, condensed readily with isatin, giving an intensely red product (III; R = H). The lactone was converted by mild alkaline hydrolysis into an unstable



(I)



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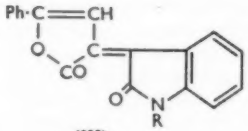

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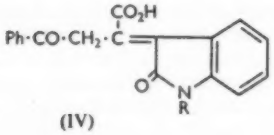

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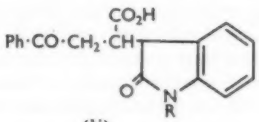

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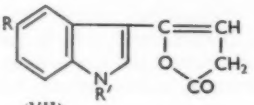

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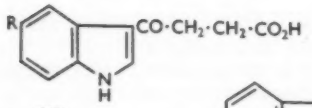
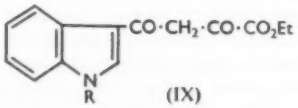
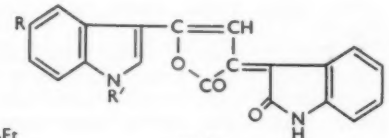


(VI)



(IX)



(VIII)

orange acid regarded as (IV; R = H) since in hot solvents it reverts to the red lactone (III; R = H). On reduction with zinc and alkali the acid (IV; R = H) gave β-benzoyl-α-3-oxindolylpropionic acid (V; R = H), a close analogue of the C_{20} acid. With hot acetic anhydride and sodium acetate, both compounds (IV; R = H) and (V; R = H) gave the red acetylated lactone (III; R = Ac) which was also obtained directly from (III; R = H) by acetylation. The conversion of the saturated acid (V; R = H) into compound (III; R = Ac) involves, not only acetylation and dehydration, but also oxidation and is exactly analogous to the behaviour of the C_{20} acid [1] under the same conditions.

An essentially similar series of experiments, with 1-methylisatin in place of isatin in the initial condensation, afforded the series (III), (IV), and (V) in which R = Me. When heated with acetic anhydride and sodium acetate, the colourless acid (V; R = Me) reverted to the red unsaturated lactone (III; R = Me).

* Part V, *J.*, 1957, 2227.

[1] Ballantine, Barrett, Beer, Boggiano, Clarke, Eardley, Jennings, and Robertson, *J.*, 1957, 2222.

By starting with indolyloxobutyric acids of type (VI) the synthetical method outlined above was obviously applicable to the preparation of compounds of type (I). In the first instance we elected, on grounds of availability, to employ the keto-acid (VI; R = H) derived from indole itself, and although this acid gave intractable products when heated with acetic anhydride, treatment with hot acetyl chloride afforded in good yield a crystalline product regarded as the lactone (VII; R = H, R′ = Ac). This lactone reacted smoothly with isatin in alcohol containing a trace of pyridine, giving the red condensation product (VIII; R = H, R′ = Ac) which, with zinc dust and alkali, was converted into γ-3-indolyl-α-3-oxindolyl-γ-oxobutyric acid (I; R = H, R′ = H).

With the 5-methoxyindolyloxobutyric acid [2] (VI; R = OMe) as starting material repetition of the synthetical procedure gave, by way of the intermediates (VII; R = OMe, R′ = Ac) and (VIII; R = OMe, R′ = Ac), the colourless acid (I; R = OMe, R′ = H) which on methylation yielded γ-(5-methoxy-1-methyl-3-indolyl)-α-(1-methyl-3-oxindolyl)-γ-oxobutyric acid (I; R = OMe, R′ = Me). This product was identical with the trimethyl derivative [1] of the C_{20} acid and was converted by the action of hot acetic anhydride containing sodium acetate into a red compound identical with the " magenta lactone ".[1] The structure (I; R = OH, R′ = H) for the C_{20} acid may therefore be regarded as firmly established.

An alternative route to compounds of type (I), which was explored without success, involved the condensation of an indolyl-αγ-dioxobutyric ester or acid, *e.g.*, (IX; R = H), with oxindole. A similar condensation, between pyruvic acid and oxindole, has been described by Julian *et al.*[3] Both 3-acetylindole and 3-acetyl-1-methylindole reacted readily with ethyl oxalate in the presence of sodium ethoxide, giving the expected products (IX; R = H) and (IX; R = Me); these were converted to the corresponding acids by alkaline hydrolysis, but neither the dioxobutyric esters nor the acids could be induced to condense in the desired manner with oxindole.

Experimental

Unless otherwise stated, the light petroleum used had b. p. 60—80°.

4-Hydroxy-2-3′-oxindolylidene-4-phenylbut-3-enoic Lactone (III; R = H).—Isatin (6·0 g.) was added to a stirred solution obtained by heating β-benzoylpropionic acid [4] (7·0 g.) with acetic anhydride (8 ml.) on the steam-bath for 2 hr. and the mixture was then heated for a further 30 min. After being washed with a little hot alcohol, the crystalline *lactone* (4·5 g.) was sufficiently pure for use in the next stage. An analytical sample was crystallised from alcohol forming deep red needles, m. p. > 260° (Found: C, 74·7; H, 4·1; N, 4·6. $C_{18}H_{11}O_3N$ requires C, 74·7; H, 3·8; N, 4·8%). The same product was obtained by the interaction of the preformed lactone [5] of β-benzoylpropionic acid with isatin in hot ethanol containing a trace of piperidine.

β-Benzoyl-α-3-oxindolylpropionic Acid (V; R = H).—On being warmed 4-hydroxy-2-3′-oxindolylidene-4-phenylbut-3-enoic lactone (3 g.) slowly dissolved in a mixture of alcohol (20 ml.) and 2N-aqueous sodium hydroxide (12 ml.); the salt of the resulting acid was kept in solution by gradual addition of hot water (40 ml.). On acidification with acetic acid the cooled filtered solution deposited a sticky solid which became crystalline when rubbed. This acid readily reverted to the lactone in hot solvents; rapid recrystallisation from ethyl acetate–light petroleum furnished the acid in orange leaflets (2 g.), m. p. 133°, which gave unsatisfactory analytical data. A solution of the acid (2 g.) in 2N-aqueous sodium hydroxide (25 ml.) and water (20 ml.) was heated and stirred with zinc dust (1 g.) until the colour of the solution changed from orange to pale yellow. The filtered solution was cooled to 0° and carefully acidified, giving *β-benzoyl-α-3-oxindolylpropionic acid* which separated from ethyl acetate–light petroleum in colourless leaflets (1·3 g.), m. p. 185—186° (Found: C, 69·7; H, 5·0; N, 4·5. $C_{18}H_{15}O_4N$ requires C, 69·9; H, 4·9; N, 4·5%). The red solution obtained by heating β-benzoyl-α-3-oxindolylpropionic acid (0·5 g.) with acetic anhydride (4 ml.) and sodium acetate (0·5 g.) for 15 min. was cooled, and the following day the crystalline deposit was collected, washed

[2] Ballantine, Barrett, Beer, Boggiano, Eardley, Jennings, and Robertson, *J.*, 1957, 2227.
[3] Julian, Printy, Ketcham, and Doone, *J. Amer. Chem. Soc.*, 1953, **75**, 5305.
[4] Martin and Fieser, *Org. Synth.*, Coll. Vol. II, p. 81.

thoroughly with warm water, and then recrystallised from acetic acid, giving 2-(1-*acetyl*-3-*oxindolylidene*)-4-*hydroxy*-4-*phenylbut*-3-*enoic lactone* (III; R = Ac) in red needles (150 mg.), m. p. 220° (Found: C, 72·5; H, 4·1; N, 3·9. $C_{20}H_{13}O_4N$ requires C, 72·5; H, 3·9; N, 4·2%). The same product was obtained by the interaction of acetic anhydride and sodium acetate with β-benzoyl-α-3-oxindolylidenepropionic acid and with 4-hydroxy-2-3′-oxindolylidene-4-phenylbut-3-enoic lactone.

β-*Benzoyl*-α-(1-*methyl*-3-*oxindolyl*)*propionic Acid* (V; R = Me).—When isatin was replaced by 1-methylisatin in the condensation described above, the product (75% yield) was 4-*hydroxy*-2-(1-*methyl*-3-*oxindolylidene*)-4-*phenylbut*-3-*enoic lactone* (III; R = Me) which crystallised from alcohol in dark red needles, m. p. 182° (decomp.) (Found: C, 75·4, 75·0; H, 4·6, 4·6; N, 4·6. $C_{19}H_{13}O_3N$ requires C, 75·3; H, 4·3; N, 4·6%). On hydrolysis with alkali this lactone (5 g.) afforded β-*benzoyl*-α-(1-*methyl*-3-*oxindolylidene*)*propionic acid* (3·8 g.), forming yellow needles, m. p. 112°, from benzene–light petroleum (Found: C, 70·7; H, 4·8; N, 4·0. $C_{19}H_{15}O_4N$ requires C, 71·0; H, 4·7; N, 4·4%). In hot solvents this acid is rapidly converted into the original lactone; reduction of the compound with zinc dust in alkaline solution gave β-*benzoyl*-α-(1-*methyl*-3-*oxindolyl*)*propionic acid* which formed colourless needles, m. p. 151°, from ethyl acetate–light petroleum (yield 70%) (Found: C, 71·0; H, 5·2; N, 4·4. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%). With boiling acetic anhydride containing sodium acetate, the last acid (600 mg.) furnished 4-hydroxy-2-(1-methyl-3-oxindolylidene)-4-phenylbut-3-enoic lactone (160 mg.), m. p. 181° (decomp.), identical with the material already described.

4-(1-*Acetyl*-3-*indolyl*)-4-*hydroxy*-2-3′-*oxindolylidenebut*-3-*enoic Lactone* (VIII; R = H, R′ = Ac).—Hot freshly distilled acetyl chloride (15 ml.) was added to γ-3-indolyl-γ-oxobutyric acid [2] (0·5 g.) and the mixture then heated under reflux for 2 hr. The resulting yellow solution was evaporated to dryness in a vacuum and, on crystallisation from light petroleum (b. p. 100—120°), the residue afforded 4-(1-*acetyl*-3-*indolyl*)-4-*hydroxybut*-3-*enoic lactone* (VII; R = H, R′ = Ac) (0·42 g.) in pale yellow needles, m. p. 155° (Found: C, 69·5; H, 4·8; N, 5·6; Ac, 17·8. $C_{12}H_8O_3N{\cdot}CO{\cdot}CH_3$ requires C, 69·7; H, 4·6; N, 5·8; Ac, 17·8%). Heated for 30 min. with isatin (55 mg.) in alcohol (7 ml.) containing one drop of pyridine, this lactone (100 mg.) gave 4-(1-*acetyl*-3-*indolyl*)-4-*hydroxy*-2-3′-*oxindolylidenebut*-3-*enoic lactone* (120 mg.) which crystallised from acetone–light petroleum in deep red needles, m. p. 285° (Found: C, 71·0; H, 3·6; N, 7·2; Ac, 11·8. $C_{20}H_{11}O_3N_2{\cdot}CO{\cdot}CH_3$ requires C, 71·4; H, 3·8; N, 7·6; Ac, 11·6%).

γ-3-*Indolyl*-α-3-*oxindolyl*-γ-*oxobutyric Acid* (I; R = R′ = H).—On being agitated with zinc dust in nitrogen the orange solution of 4-(1-acetyl-3-indolyl)-4-hydroxy-2-3′-oxindolylidenebut-3-enoic lactone (100 mg.) in hot 1·5N-aqueous sodium hydroxide rapidly became pale yellow and 2 min. later the mixture was filtered, the residue was washed with water, and the combined filtrate and washings were cooled to −5°, made slightly acid (pH 6·5), and filtered. Acidification of the filtrate to pH 2 precipitated a white solid which on crystallisation from ethyl acetate–light petroleum and then from ethyl acetate gave γ-3-*indolyl*-α-3-*oxindolyl*-γ-*oxobutyric acid* in colourless plates (75 mg.), m. p. 235° (decomp.) (Found: C, 68·8; H, 4·8; N, 7·9. $C_{20}H_{16}O_4N_2$ requires C, 69·0; H, 4·6; N, 8·0%).

4-(1-*Acetyl*-5-*methoxy*-3-*indolyl*)-4-*hydroxy*-2-3′-*oxindolylidenebut*-3-*enoic Lactone* (VIII; R = OMe, R′ = Ac).—Treated with boiling acetyl chloride (10 ml.) for 2 hr., γ-(5-methoxy-3-indolyl)-γ-oxobutyric acid [2] (250 mg.) afforded 4-(1-*acetyl*-5-*methoxy*-3-*indolyl*)-4-*hydroxybut*-3-*enoic lactone*, which crystallised from light petroleum (b. p. 100—120°) in yellow needles (180 mg.), m. p. 159° (Found: C, 66·5; H, 4·8; N, 5·2. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%). This lactone (400 mg.) and isatin (220 mg.) in hot alcohol (15 ml.), containing one drop of pyridine, gave 4-(1-*acetyl*-5-*methoxy*-3-*indolyl*)-4-*hydroxy*-2-3′-*oxindolylidenebut*-3-*enoic lactone* (480 mg.), forming deep red needles from acetone, m. p. 310° (decomp.) (Found: C, 68·8; H, 4·3; N, 6·5. $C_{23}H_{16}O_5N_2$ requires C, 69·0; H, 4·0; N, 6·7%).

γ-(5-*Methoxy*-1-*methyl*-3-*indolyl*)-α-(1-*methyl*-3-*oxindolyl*)-γ-*oxobutyric Acid* (I; R = OMe, R′ = Me).—Reduction of 4-(1-acetyl-5-methoxy-3-indolyl)-4-hydroxy-2-3′-oxindolylidenebut-3-enoic lactone (150 mg.), dissolved in 1·5N-aqueous sodium hydroxide (15 ml.) at 100°, with zinc dust (300 mg.) in the absence of air gave γ-(5-methoxy-3-indolyl)-α-3′-oxindolyl-γ-oxobutyric acid (80 mg.) as an off-white amorphous powder which could not be satisfactorily crystallised. Addition of methyl sulphate (1·0 ml.), in portions (0·2 ml.), to a warm agitated solution of the oxobutyric acid (50 mg.) in 2N-aqueous sodium hydroxide (7 ml.) (in nitrogen) during 30 min. gave, after acidification of the cooled mixture, γ-(5-*methoxy*-1-*methyl*-3-*indolyl*)-α-(1-*methyl*-3-*oxindolyl*)-γ-*oxobutyric acid* which was washed with cold acetone and then crystallised from

acetone, forming colourless plates (45 mg.), m. p. 266° (decomp.) (Found: C, 68·0; H, 5·4; N, 6·8. $C_{23}H_{22}O_5N_2$ requires C, 68·0; H, 5·4; N, 6·9%). This product was shown to be identical with the trimethyl derivative [1] of the C_{20} acid from violacein by mixed m. p. determination, by comparison of ultraviolet and infrared absorption spectra, and by its conversion by hot acetic anhydride and sodium acetate into 4-hydroxy-4-(5-methoxy-1-methyl-3-indolyl)-2-(1-methyl-3-oxindolylidene)-but-3-enoic lactone, identical in infrared absorption and other respects with the " magenta lactone ".[1]

Ethyl γ-3-Indolyl-αγ-dioxobutyrate (IX; R = H).—A mixture of ethyl oxalate (3·2 g.) and 3-acetylindole [6] (3·2 g.), alcohol (40 ml.), and sodium ethoxide (from 0·5 of sodium) was heated under reflux for 10 hr., concentrated in a vacuum, and acidified with 2N-sulphuric acid at 0°. The addition of ice-cold water completed the precipitation of *ethyl γ-3-indolyl-αγ-dioxobutyrate* which separated from aqueous alcohol in yellow leaflets (2·9 g.), m. p. 192° (Found: C, 64·8; H, 5·1; N, 5·5. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%).

Ethyl γ-(1-Methyl-3-indolyl)-αγ-dioxobutyrate (IX; R = Me).—3-Acetylindole (5 g.), in acetone (50 ml.), was mixed with potassium hydroxide (30 g.) in water (18 ml.), then methyl sulphate (25 ml.) was gradually introduced to the agitated mixture during 30 min. 30 Min. later the mixture was poured into water, and the product, *3-acetyl-1-methylindole*, recrystallised from light petroleum forming colourless feathery needles (4·8 g.), m. p. 109—110° (Found: C, 76·3; H, 6·2; N, 8·1. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%). A solution of 3-acetyl-1-methylindole (3·5 g.) and ethyl oxalate (3·2 g.) in benzene (25 ml.) was heated with sodium ethoxide (from 0·3 g. of sodium) for 7 hr. The yellow salt was collected, washed with benzene and ether, and decomposed with hot aqueous acetic acid. On cooling, the solution deposited *ethyl γ-(1-methyl-3-indolyl)-αγ-dioxobutyrate* which crystallised from acetic acid in yellow needles (3·6 g.), m. p. 122° (Found: C, 66·3; H, 5·5; N, 5·1. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5; N, 5·1%).

γ-3-Indolyl-αγ-dioxobutyric Acid.—Ethyl γ-3-indolyl-αγ-dioxobutyrate (200 mg.), alcohol (5 ml.), and 2N-aqueous sodium hydroxide (0·5 ml.) were heated on the steam-bath for 10 min. and poured into water (30 ml.). Acidification then gave the *acid* which separated from acetic acid in yellow leaflets (150 mg.), m. p. 220 (Found: C, 62·1; H, 3·7; N, 6·4. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9; N, 6·1%). Similarly prepared, *γ-(1-methyl-3-indolyl)-αγ-dioxobutyric acid* crystallised from acetic acid in yellow needles, m. p. 120° (Found: C, 64·0; H, 4·8; N, 5·3. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates in this Department.

UNIVERSITY OF LIVERPOOL. [*Received, June 21st,* 1957.]

[5] Kugel, *Annalen*, 1898, **299**, 54.
[6] Saxton, *J.*, 1952, 3592.

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970. *Steroids. Part XIV.* Some 3β-Fluoro-steroids.*

By C. W. SHOPPEE and G. H. R. SUMMERS.

3 : 5-*cyclo*Stan-6-ols are rearranged by hydrofluoric acid in benzene to the appropriate 3β-fluoro-steroids.

IT was found by Heilbron, Beynon, and Spring [1] and by Wallis and Ford [2] that 3 : 5-*cyclo*cholestan-6β-ol, its methyl ether, and its acetate (I; R = H, Me, or Ac), on treatment with hydrogen chloride, bromide, or iodide in acetic acid at 20° readily afford the mesomeric cation (II) [3-6] which, under these conditions, by thermodynamic control of the equilibria,[6]

* Part XIII, *J.*, 1957, 3107.

[1] Heilbron, Beynon, and Spring, *J.*, 1936, 907; 1937, 1459.
[2] Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415.
[3] Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424.
[4] Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Winstein and Schlesinger, *ibid.*, p. 3528; Winstein and Kosower, *ibid.*, 1956, **78**, 4347.
[5] Wagner and Wallis, *ibid.*, 1950, **72** 1047; Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529; Wolff and Wallis, *ibid.*, p. 1361.
[6] Shoppee and Summers, *J.*, 1952, 3361; Shoppee and Williams, *J.*, 1956, 2488.

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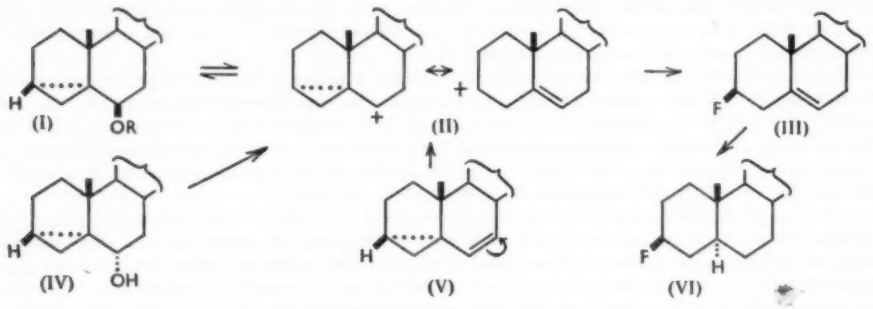
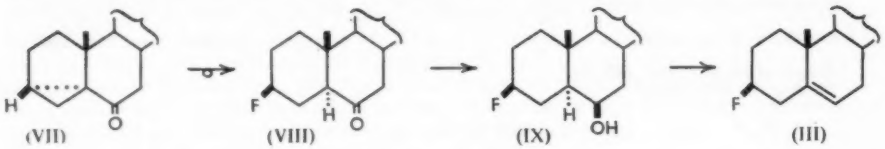
gives the appropriate cholesteryl halide (as III) in high yield. Similarly, 3 : 5-*cyclo*-cholestan-6α-ol [5,6] (IV) and 3 : 5-*cyclo*cholest-6-ene [7] (V) with hydrogen chloride, bromide, or iodide in acetic acid at 20° furnish the cholesteryl halides in good yield. Some seven



years ago we applied these methods to the preparation of cholesteryl fluoride (III), and we now record this and two other examples.

3 : 5-*cyclo*-5α-Cholestan-6β-ol (I; R = H) with 40% hydrofluoric acid in benzene gives cholesterol (22%) and cholesteryl fluoride (III) (76%), hydrogenated with platinum in ethyl acetate containing a trace of perchloric acid to cholestanyl fluoride (VI). Use of hydrofluoric acid in acetic acid gave only cholesteryl acetate. Cholesteryl fluoride was also obtained from 6β-methoxy-3 : 5-*cyclo*cholestane (I; R = Me) and from 3 : 5-*cyclo*cholestan-6α-ol (IV) by treatment with hydrofluoric acid in ether–acetic acid. 6β-Methoxy-3 : 5-*cyclo*cholestane (I; R = Me) has recently been converted by treatment with anhydrous hydrogen fluoride in acetic acid into cholesteryl fluoride (III), accompanied by cholesteryl acetate, by Jacobsen and Jensen [8] who, using silver fluoride in xylene–methyl cyanide, also obtained cholesteryl fluoride from cholesteryl iodide by substitution (S_Ni) with retention of configuration, as the result of participation by the π-electrons of the double bond.

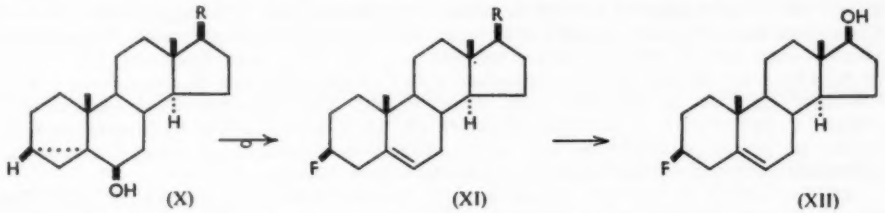


Cholesteryl fluoride was obtained on a single occasion from 3 : 5-*cyclo*cholestan-6-one (VII) by treatment with hydrofluoric acid in ether–acetic acid, reduction of the resulting product (VIII?) with lithium aluminum hydride in ether, and dehydration of the material so produced (IX?) with phosphorus oxychloride–pyridine.[9,10] Satisfactory analyses of the intermediates could not be obtained, and several attempts to repeat the procedure were unsuccessful; the 3 : 5-*cyclo*-ketone (VII) is unchanged by hydrofluoric acid in benzene, and with hydrofluoric acid in acetic acid appears to yield only 3β-acetoxycholestan-6-one.

Solvolysis of 3β-toluene-*p*-sulphonyloxypregn-5-en-20-one [11] with aqueous acetone in presence of potassium acetate yields 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one [11] (X; R = Ac). Treatment of this and of 6β-hydroxy-3 : 5-*cyclo*androstan-17-one (X; R = O) [12]

[7] Riegel, Hager, and Zenitz, *J. Amer. Chem. Soc.*, 1946, **68**, 2562.
[8] Jacobsen and Jensen, *Chem. and Ind.*, 1957, 172.
[9] Shoppee, Reilly Lectures, Univ. of Notre Dame, 1951.
[10] Shoppee and Summers, *J.*, 1952, 1786.
[11] Butenandt and Grosse, *Ber.*, 1937, **70**, 1446; Karrer, Asmis, Sareen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022; Patel, Petrow, and Stuart-Webb, *J.*, 1957, 665.
[12] Butenandt and Suranyi, *Ber.*, 1942, **75**, 591; Dingemanse, Huis in't Veld, and Hartogh-Katz, *Nature*, 1948, **162**, 492; Barton and Klyne, *ibid.*, p. 493.

with hydrofluoric acid in benzene gives 3β-fluoropregn-5-en-20-one (XI; R = Ac), accompanied by pregnenolone, and 3β-fluoroandrost-5-en-17-one (XI; R = O) respectively. These compounds have also been prepared by Jacobsen and Jensen [8] from 3β-iodopregn-5-en-20-one and 3β-iodoandrost-5-en-17-one by reaction with silver fluoride.



(X) (XI) (XII)

By reduction with lithium aluminium hydride or sodium borohydride, 3β-fluoroandrost-5-en-17-one affords 3β-fluoroandrost-5-en-17β-ol (XII).

Experimental

For general directions see *J.*, 1957, 3107. $[\alpha]_D$ are in $CHCl_3$.

3β-*Fluorocholest-5-ene*.—(*a*) 3 : 5-*cyclo*Cholestan-6β-ol (m. p. 74°; 1 g.) in benzene (30 c.c) was treated with 40% hydrofluoric acid (20 c.c.) in a Polythene flask at 20° for 4 hr. The mixture was poured into 4N-sodium hydroxide, and the product extracted with ether and worked up in the usual way to give an oil, which was chromatographed on aluminium oxide (Spence type H, activity ~II; 30 g.). Elution with pentane gave 3β-fluorocholest-5-ene (760 mg.), m. p. 94—96°, $[\alpha]_D$ −45·5° (*c* 1·4), after recrystallisation from acetone (cf. ref. 8) (Found: C, 83·4; H, 11·4. Calc. for $C_{27}H_{45}F$: C, 83·45; H, 11·65%), giving a yellow colour with tetranitromethane and a negative Beilstein test; elution with ether gave cholesterol (224 mg.), m. p. and mixed m. p. 148° after recrystallisation from ethyl acetate. When 3 : 5-*cyclo*cholestan-6β-ol (835 mg.) was treated similarly in "AnalaR" acetic acid (30 c.c.), the sole product appeared to be cholesteryl acetate; it was hydrolysed with hot 5N-methanolic potassium hydroxide for 0·5 hr. and the resulting solid chromatographed on aluminium oxide (25 g.); elution with pentane gave a trace of oil (8 mg.), and elution with chloroform gave cholesterol (823 mg.), m. p. and mixed m. p. 146—148°.

(*b*) 6β-Methoxy-3 : 5-*cyclo*cholestane (m. p. 79°) in ether was treated with 40% hydrofluoric acid and a little acetic acid added to give a homogeneous solution. The usual working up gave 3β-fluorocholest-5-ene, m. p. 94° after crystallisation from ethanol.

(*c*) 3 : 5-*cyclo*Cholestan-6α-ol (m. p. 79—80°) by similar treatment with 40% hydrofluoric acid in ether containing acetic acid gave 3β-fluorocholest-5-ene, m. p. 91—94°, and cholesteryl acetate; the latter was separated by hydrolysis to cholesterol followed by chromatography on aluminium oxide.

(*d*) 3 : 5-*cyclo*Cholestan-6-one (m. p. 96°; 450 mg.) in ether containing acetic acid with 40% hydrofluoric acid gave, on a single occasion by the usual working up, a substance, m. p. 136° after crystallisation from acetone (Found: C, 62·5; H, 8·4%), converted by treatment with lithium aluminium hydride in ether at 36° into a substance, m. p. 110° after crystallisation from methanol–ethyl acetate (Found: C, 63·5; H, 8·9%), which was dehydrated by phosphorus oxychloride in pyridine at 20° to 3β-fluorocholest-5-ene, m. p. and mixed m. p. 90—94°. Attempts to repeat this preparation of the substance, m. p. 136°, with new specimens of hydrofluoric acid in acetic acid invariably gave 3β-acetoxycholestan-6-one, m. p. 129—130°. When 3 : 5-*cyclo*cholestan-6-one (1·7 g.) was treated with 40% hydrofluoric acid (20 c.c.) in benzene (20 c.c.) for 24 hr. and the product chromatographed on aluminium oxide (60 g.) to give seven fractions by elution with pentane, benzene–pentane (1 : 9), and benzene, all fractions had m. p. 94—96°, with $[\alpha]_D$ +41° (*c* 1·8), +39° (*c* 1·2), and +40° (*c* 1·4) for fractions 1, 4, and 7 respectively, and consisted of unchanged 3 : 5-*cyclo*cholestan-6-one.

3β-*Fluorocholestane*.—3β-Fluorocholest-5-ene (200 mg.), in ethyl acetate (20 c.c.) containing 4 drops of 60% perchloric acid, was hydrogenated with platinum oxide (70 mg.). Reduction was complete in 5 min. and the usual working up gave an oil which crystallised. To remove any unsaturated material the product was warmed with a 2% solution of chromium trioxide in

acetic acid (7 c.c.) at 60° for 0·5 hr.;[13] the saturated material was extracted with ether, washed with 2N-sodium carbonate and with water, and dried. The product (196 mg.), in pentane, was filtered through aluminium oxide and crystallised from acetone, to give 3β-*fluorocholestane*, m. p. 80—82°, $[\alpha]_D$ +23° (*c* 1·0) (Found: C, 82·75; H, 11·8. $C_{27}H_{47}F$ requires C, 83·0; H, 12·1%).

3β-*Fluoropregn*-5-*en*-20-*one*.—Solvolysis of 3β-toluene-*p*-sulphonyloxypregn-5-en-20-one (m. p. 141°)[11] with aqueous acetone in presence of potassium acetate furnished 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one, m. p. 181—182°, $[\alpha]_D$ +124° (*c* 1·0), after crystallisation from acetone. The 3 : 5-*cyclo*-alcohol (440 mg.) in benzene (20 c.c.) with 40% hydrofluoric acid (10 c.c.) at 20° for 4 hr., after the usual isolation procedure, gave 3β-fluoropregn-5-en-20-one (295 mg.), m. p. 170—172° (lit.,[8] m. p. 164—165°), $[\alpha]_D$ +114° (*c* 1·27) after recrystallisation from acetone (Found: C, 79·1; H, 9·5. Calc. for $C_{21}H_{31}OF$: C, 79·2; H, 9·8%), and 3β-hydroxypregn-5-en-20-one, m. p. and mixed m. p. 192—194°, which were separated by chromatography on aluminium oxide and elution with benzene and chloroform, respectively.

3β-*Fluoroandrost*-5-*en*-17-*one*.—6β-Hydroxy-3 : 5-*cyclo*androstan-17-one[12] (m. p. 140°; 734 mg.) in benzene (20 c.c.) was treated with 40% hydrofluoric acid at 20° for 3 hr. The usual working up gave a solid, which was purified by chromatography on aluminium oxide (20 g.); elution with benzene gave 3β-fluoroandrost-5-en-17-one (506 mg.), m. p. 154—155°, $[\alpha]_D$ −19° (*c* 1·0), after crystallisation from ethyl acetate and recrystallisation from acetone (Found: C, 78·4; H, 9·5. Calc. for $C_{19}H_{27}OF$: C, 78·6; H, 9·3%) (cf. ref. 8). Elution with ether gave 3β-hydroxyandrost-5-en-17-one, m. p. 153° (260 mg.).

3β-*Fluoroandrost*-5-*en*-17β-*ol*.—3β-Fluoroandrost-5-en-17-one (60 mg.) was reduced with lithium aluminium hydride in ether at 36° for 15 min. The solid product, isolated in the usual manner, by recrystallisation from acetone, gave 3β-*fluoroandrost*-5-*en*-17β-*ol*, m. p. 160—162°, $[\alpha]_D$ −60° (*c* 0·8) (Found: C, 78·0; H, 9·7. Calc. for $C_{19}H_{29}OF$: C, 78·05; H, 10·0%) (cf. ref. 8).

We thank Glaxo Laboratories Limited, British Drug Houses Limited, and Organon Chemicals Limited for gifts of cholesterol, pregnenolone, and dehydro*epi*androsterone, respectively.

UNIVERSITY COLLEGE, SWANSEA, THE UNIVERSITY OF WALES.
THE UNIVERSITY OF SYDNEY, AUSTRALIA. [*Received, June 28th*, 1957.]

[13] Shoppee, *J.*, 1946, 1151.

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971. 2 : 3-*Derivatives of Naphthalene. Part III.*[1] *The Electrophilic Substitution Reactions of* 3-*Nitro*-2-*naphthylamine and* N-*Acylated Derivatives.*

By E. R. WARD, T. M. COULSON, and P. R. WELLS.

Diazo-coupling, chlorination, bromination, and nitration of 3-nitro-2-naphthylamine, and several of its *N*-acyl derivatives, have been studied. Nitro-groups can be introduced at the 1-, 5-, 6-, or 8-position.

Some general features of electrophilic substitution of naphthalene derivatives, in contrast to those of benzene derivatives, are discussed.

Diazo-naphthol formation by a variety of 1-substituted 3-nitro-2-naphthylamines and 1 : 3 : *x*-trinitro-2-naphthylamines always occurs by nucleophilic displacement of a group at the 1-position, forming a 1 : 2-diazonaphthol. This confirms the apparent impossibility of forming a 2 : 3-diazonaphthol structure.

1 : 6 : 7-Trinitronaphthalene has been synthesised and found to be identical with the mononitration product of 2 : 3-dinitronaphthalene.

CONTINUING our investigation of electrophilic substitution of nitronaphthylamines we now present semiquantitative data for 3-nitro-2-naphthylamine, which are summarised in Table 1.

Present interest in aromatic electrophilic substitution largely centres on the efforts to place the simplest possible cases on a quantitative theoretical base, namely, benzene

[1] Part II, Ward and Coulson, *J.*, 1954, 4545.

derivatives [2] and unsubstituted polycyclic aromatic hydrocarbons.[3] Naphthalene derivatives present more complex problems since there is a wider variety of possible substitutions and the modifying effects of substituents are more subtle, wherein lies the value of studies in this field.

Our tentative general analysis [4] of the effects of substituents in the 1- or 2-position of naphthalene compounds on other ring positions, as compared with a similar analysis for

TABLE 1. *Position of substitution (with, in parentheses, yields †) of 3-nitro-2-naphthylamine and its acyl derivatives.*

Reaction	Conditions	Amine	Acyl $CH_3{\cdot}CO$	Acyl p-$C_6H_4Me{\cdot}SO_2$	Acyl m-$NO_2{\cdot}C_6H_4{\cdot}SO_2$	Acyl o-$C_6H_4(CO)_2$
Diazo-coupling	Aq. EtOH	1 (95%)	—	—	—	—
Chlorination	AcOH, 50°	—	1 (80%)	—	—	—
Bromination	$CHCl_3$, room temp.	1 (100%), 1 : 6 (88%)	—	—	—	—
	AcOH, b. p.	—	1 (95%)	—	—	—
Nitration	A	—	—	1 (84%)	1 (53%)	—
Nitration	B	—	1, 6, 8 (75%), (15 : 2 : 3)	—	—	—
Nitration	C	—	1 : 5, 1 : 8 (85%) (19 : 16)	—	1 : 6 (55%) *	5, 8 (70%) (39 : 35)

A, nitric acid (d 1·5)–acetic acid at 80°. B, nitric acid (d 1·5)–acetic acid–boron trifluoride at 80°. C, nitric acid (d 1·5) at −5°. * At 20°.

† Yields refer to isolated products, when necessary after hydrolysis, and usually after chromatography.

benzene compounds, is given in Table 2. The relative strengths are given in terms of each effect separately and are not intended to show any particular relationship between effects. Where no strength is indicated it is assumed that the effect is negligible. The steric effect (S) is represented as equivalent at all positions "*ortho*" to the substituent, although it is likely from a consideration of the geometry of the naphthalene system [5] that in finer detail the effects are in the order 8 > 2, and 1 > 3 for 1- and 2-substituents respectively.

TABLE 2. *Relative strengths of the various reactivity-determining factors due to a single substituent* X *in the benzene or naphthalene nucleus.*

	1-$C_{10}H_7X$				2-$C_{10}H_7X$				C_6H_5X		
Posn.	I	T	S	Posn.	I	T	S	Posn.	I	T	S
2	++	++	+	1	++	++	+	*o*	++	+	+
3	+	δ+		3	++	+	+	*m*	+	δ+	
4	+	++		4	+			*p*	+	+	
5	δ+	+		5	δ+						
6	δ+			6	δ+	+					
7	δ+	+		7	δ+						
8	+		+	8	δ+	+					

I = inductive; T = tautomeric; S = steric. ++ Very strong; + strong; δ+ weak.

To apply to naphthalene a treatment similar to that given by H. C. Brown [3] to benzene derivatives, further physical data are required similar to those reported by Price and by Bryson [4] and, for our work, further substituent constants for other acylated amino-groups.

It is not possible to discuss fully the effect of acylation on the directing influence

[2] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 1913, and references therein.

[3] Dewar, Mole, and Warford, *J.*, 1956, 3581 and references therein.

[4] Cf. Roberts, Clement, and Drysdale, *J. Amer. Chem. Soc.*, 1951, **73**, 2181; Taft in Newman's "Steric Effects in Organic Chemistry," John Wiley & Sons, New York, 1956, Chap. XIII; Jaffe, *Chem. Rev.*, 1953, **53**, 191; Price and Michel, *J. Amer. Chem. Soc.*, 1952, **74**, 3652; Price, Mertz, and Wilson, *ibid.*, 1954, **76**, 1531; Bryson, *Trans. Faraday Soc.*, 1949, **45**, 257; 1950, **46**, 528; Dewar in Cook's "Progress in Organic Chemistry," Butterworths, London, 1953, Vol. II, pp. 1—28.

[5] Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 233.

of the amino-group in aromatic electrophilic substitution until more experimental facts and theoretical treatments are available. *E.g.*, the phthalimido-group has previously been considered to be a simple *o*/*p*-directing group [6,7] but the data for naphthalene compounds [8] suggest that it exerts a deactivating influence comparable to that of a halogen atom. Nevertheless certain valid comments can already be made.

Our results for 2-naphthylamines illustrate the selectivity of the weaker electrophilic reagents (*e.g.*, polarised halogen molecules), which give a single monosubstitution product, in contrast to the more powerful nitrating agents which give mixed products (cf. H. C. Brown [2]). This however is not so obvious as with 2- or 4-substitution in a 1-naphthylamine derivative, presumably because in a 2-naphthylamine derivative the 1-position is normally by far the most activated, whereas the 2- and the 4-position in the 1-substituted compound may not differ greatly in reactivity—for a 1-naphthylamine (+*T*) derivative it can no longer be accepted that the 4-position is always the most activated (cf. Ingold; [6b] Ward and Coulson; [9] Hardy and Ward [8] for the nitration of 7-nitro-*N*-toluene-*p*-sulphonyl-1-naphthylamine; Hodgson and Turner [10] for the monobromination of 5-nitro-1-naphthylamine).

The reactivities of 8- and 3-nitro-2-naphthylamine and their *N*-acyl derivatives in electrophilic substitution are similar: both amines are considerably less reactive than β-naphthylamine itself and slightly less reactive than 4-nitro-2-naphthylamine (*e.g.*, the *N*-toluene-*p*-sulphonyl derivative of the latter can be dinitrated [11]). For 3-nitro-2-naphthylamine this can be attributed to weakening of the activating influence of the 2-amino-group by the adjacent 3-nitro-group.

The dinitration of *N*-acetyl-3-nitro-2-naphthylamine by fuming nitric acid requires to be considered in the light of possible salt formation at the amido-group (cf. Ward and Coulson [9]). Since we find that *N*-acetyl-1 : 3-dinitro-2-naphthylamine is not further nitrated under these conditions, nitration must occur at the 5- and 8-positions before the 1-position is attacked. This indicates that salt formation does occur and that substitution takes place at the less deactivated α-positions in the other nucleus (this is analogous to the formation of the 1 : 6 : 7-trinitronaphthalene on mononitration of 2 : 3-dinitronaphthalene [12] and to the nitration of *N*-phthaloyl-3-nitro-2-naphthylamine reported above). This salt formation must be substantially complete since, if any neutral form were present, nitration would take place through this form and in a different manner from that found. Further, one must tentatively postulate that introduction of a second nitro-group so reduces the basicity of the acetamido-group that some of the neutral form is present which is nitrated further at the 1-position (cf. also Dewar [13]).

As regards the orientation of our products we need only comment on the three trinitronaphthylamines. All these yielded diazo-naphthols, confirming the presence of a nitro-group in the 1-position. 1 : 3 : 5- and 1 : 3 : 8-Trinitro-2-naphthylamines were identical with the amines arising from the nitration of *N*-acetyl-3 : 5- and -3 : 8-dinitro-2-naphthylamine respectively. The third trinitro-amine must be 1 : 3 : *x*-trinitro-2-naphthylamine, where $x = 4$, 6 or 7. Position 4 can reasonably be excluded and it is almost certain that $x = 6$ by analogy with the electrophilic substitution of 2-naphthylamine derivatives.

We have assumed above that in diazo-naphthol formation for 1-substituted 3-nitro-2-naphthylamines and 1 : 3 : *x*-trinitro-2-naphthylamines only the group in the 1-position is replaced and that the alternative formation of a 2 : 3-diazonaphthol is impossible. This is supported by the fact that neither 3-amino-2-naphthol nor its 7-sulphonic acid appears

[6] Ingold, "Structure and Mechanism in Organic Chemistry," Bell & Sons, London, 1953, pp. (*a*) 239—240, (*b*) 264—266.
[7] Brady, Quick, and Welling, *J.*, 1925, 2264.
[8] Hodgson and Crook, *J.*, 1936, 1844; Hardy and Ward, *J.*, 1957, 2634.
[9] Ward and Coulson, *J.*, 1954, 4541.
[10] Hodgson and Turner, *J.*, 1942, 723.
[11] Hodgson and Hathaway, *J.*, 1945, 453.
[12] Ward and Coulson, unpublished work.
[13] Dewar, *J.*, 1949, 463.

to form a diazo-naphthol [14] and that diazotised 3-nitro-2-naphthylamine does not form one even under the most favourable conditions. The fact that a 2 : 3-diazonaphthol structure cannot be formed seems to be another consequence of the weak interaction between 2- and 3-positions in naphthalene compounds.

1 : 6 : 7-Trinitronaphthalene was prepared by a diazo-decomposition from either 3 : 5- or 3 : 8-dinitro-2-naphthylamine and was identical with the mononitration product of 2 : 3-dinitronaphthalene,[12] thus orientating the latter.

We have re-investigated the nitration of *N*-acetyl-3-chloro-1-naphthylamine and find it to be much more complex than originally described.[15] The only satisfactory product we obtained was an *N*-acetyl-chlorodinitronaphthylamine which we did not orientate. Further, our authentic 2-chloro-3-nitronaphthalene, prepared by diazo-decomposition from 3-nitro-2-naphthylamine, was not identical with that previously described.[15,16]

Experimental

N.B. 1 : 3-Dinitro-2-naphthylamine has an irritant action on the skin, especially round the mouth, nose, and eyes; the effects persist for some minutes with disturbance of the senses of taste and smell.

Ultraviolet absorption spectra of 3-nitro-2-naphthylamine and related compounds were recorded as described by Hardy and Ward [8] for EtOH media. Maxima (mμ) and, in parentheses, log *E* were:

3-Nitro-2-naphthylamine, 234 (4·56), 260 (4·25), 330 (3·79), 470 (3·29) (the maximum at 470 mμ is noteworthy in comparison with spectra of other nitronaphthylamines).

1 : 3-Dinitro-2-naphthylamine, 229 (4·55), 255 sh (4·53), 268 sh (4·41), 330 (3·95), 453 (3·66).

3 : 5-Dinitro-2-naphthylamine, 224 (4·30), 252 sh (4·43), 268 sh (4·35), 319 (3·84), 471 (3·47).

3 : 8-Dinitro-2-naphthylamine, 228 (4·27), 258 (4·49), 316 sh (3·89), 370 sh (3·33), 480 (3·63).

N-Acyl Derivatives of 3-Nitro-2-naphthylamine.—(*a*) The amine (1 g.) and phthalic anhydride (1·2 g.) were refluxed in acetic acid (10 c.c.) for 1 hr., water (70 c.c.) was added, and the mixture re-boiled; on cooling, *3-nitro-*N*-phthaloyl-2-naphthylamine* separated (1·57 g., 93%); it formed red needles, m. p. 239—240°, from acetic acid (Found: C, 67·6; H, 3·2. $C_{18}H_{10}O_4N_2$ requires C, 67·9; H, 3·2%).

(*b*) The amine (1 g.) was intimately ground with toluene-*p*-sulphonyl chloride (5 g., 5 mols.), and the mixture stirred into cold water and slowly brought to the b. p., solid sodium carbonate being stirred in from time to time to keep the liquid alkaline. After 1 hour's boiling the mixture was cooled and neutralised (litmus) with hydrochloric acid, and the solids were collected and repeatedly extracted with warm (5% w/v) aqueous potassium hydroxide. This extract on acidification yielded *3-nitro-*N*-toluene-*p*-sulphonyl-2-naphthylamine* (0·8 g., 44%), orange needles (from ethanol), m. p. 187—189° (Found: S, 9·2. $C_{17}H_{14}O_4N_2S$ requires S, 9·4%). From the alkali-insoluble residue 3-nitro-2-naphthylamine (0·5 g., 50%) was recovered by extraction with boiling 10% w/v hydrochloric acid.

(*c*) The reactants as in (*b*) were heated in pyridine (20 c.c.) on the steam-bath for 2 hr., the mixture was poured into 10% w/v hydrochloric acid (300 c.c.), and the solid was collected and worked up as before, giving almost identical yields. This experiment with 10 mols. of toluene-*p*-sulphonyl chloride gave amine (60%) and *3-nitro-*NN*-ditoluene-*p*-sulphonyl-2-naphthylamine* (30%), the monoamide apparently being absent. The diamide had m. p. 230—234° (from acetic acid) (Found: S, 13·0. $C_{24}H_{20}O_6N_2S_2$ requires S, 12·9%).

(*d*) The amine (1 g.) and *m*-nitrobenzenesulphonyl chloride (2 g., *ca.* 2 mols.) were heated together on the steam-bath for 2 hr. Unchanged amine was extracted from the powdered product by warm 10% w/v hydrochloric acid (500 c.c.), and the residue triturated with warm 10% w/v aqueous sodium hydroxide (2 × 100 c.c.), then with warm water (2 × 100 c.c.). Acidification of this extract gave *3-nitro-*N*-m-nitrobenzenesulphonyl-2-naphthylamine* [from acetic acid (charcoal)], m. p. 212° (0·28 g., 22%) (Found: C, 51·4; H, 3·2. $C_{16}H_{11}O_6N_3S$ requires C, 51·5; H, 3·0%). From the original acid extract unchanged amine (*ca.* 10%) was

[14] Goldstein and Gardiol, *Helv. Chim. Acta*, 1937, **20**, 516; Cassela, B.P. 28,107/1897.

[15] Hodgson and Elliott, *J.*, 1936, 1151.

[16] Hodgson and Hathaway, *J.*, 1945, 841; cf. Ufimtsev and Manachkina, *Doklady Akad. Nauk. S.S.S.R.*, 1953, **92**, 581.

recovered but crystallisation from acetic acid of the residues from the alkali extract only yielded material which appeared to be mixed mono- and di-amide. Yields were variable, and even lower if the reaction was carried out in pyridine.

Diazotisation and Diazo-reactions of 3-*Nitro*-2-*naphthylamine*.—(a) *Diazotisation in aqueous medium*. The amine (1 g.) was stirred into hot 10% w/v aqueous sulphuric acid (7·5 c.c.), the mixture cooled to 0°, crushed ice (2 g.) added and then sodium nitrite (0·6 g.) in the minimum amount of water rapidly with vigorous stirring.

(b) *Diazotisation in sulphuric–acetic acid*. The amine (1 g.) was dissolved in sulphuric acid (*d* 1·84, 4 c.c.) and to this was added a solution of sodium nitrite (0·4 g.) in sulphuric acid (*d* 1·84, 2·5 c.c.). This mixture was then stirred into acetic acid (13 c.c.) below 30°.

(c) 2-*Chloro*-3-*nitronaphthalene*. The diazo-solution prepared as in (b) was added to a solution of cuprous chloride (2 g.) in hydrochloric acid (*d* 1·2; 10 c.c.) and after 24 hr. the solids were collected, washed with water, dried, and refluxed with ethanol (50 c.c.; charcoal) for 30 min. The filtered extract, on concentration to 10 c.c., yielded 2-chloro-3-nitronaphthalene (0·72 g., 65%), m. p. 71—72° [from light petroleum (b. p. 100—120°)] (Found: Cl, 17·5; N, 7·0. Calc. for $C_{10}H_6O_2NCl$: Cl, 17·1; N, 6·7%). The m. p. was unchanged by steam-distilling the product or further recrystallisation from light petroleum (cf. Hodgson and Elliott [18] who give m. p. 94·5°).

(d) 2 : 3-*Dinitronaphthalene*. The diazo-solution prepared as in (a) was poured on chalk (1·2 g.) and ice (2 g.) with a little silicone antifoam and stirred vigorously. The mixture was then *immediately* added to a mixture prepared by adding a solution of crystalline copper sulphate (6·5 g.) in water (25 c.c.) to one of crystalline sodium sulphite (6·5 g.) in water (50 c.c.) and just before the reaction adding sodium nitrite (13 g.), dissolved in water (25 c.c.). The whole was stirred for 1 hr., the solid collected, washed with water, and dried, and the product obtained by extraction with boiling ethanol (charcoal) [yield 70%; m. p. 172—174° (Ward and Coulson [1] give m. p. 172—174°)].

Azo-coupling to 3-*Nitro*-2-*naphthylamine*.—*p*-Nitroaniline (0·74 g.) in hot 25% w/w aqueous sulphuric acid (3 g.) was poured into ice-water (5 g.), further ice (3 g.) added, and the whole treated rapidly with sodium nitrite (0·6 g.) in water (2 c.c.). Excess of nitrous acid was removed with sulphamic acid, and the filtered diazo-solution added, with stirring, to the amine (1 g.) in ethanol (220 c.c.), containing sodium acetate (1·4 g.). After 1 hr. the precipitated 3-*nitro*-1-p-*nitrophenylazo*-2-*naphthylamine* was collected and washed with ethanol (30 c.c.) and much hot water (yield 1·7 g., 95%). Recrystallised from hot nitrobenzene the dye had m. p. 240° (Found: C, 56·8; H, 3·5. $C_{16}H_{11}O_4N_5$ requires C, 56·7; H, 3·3%).

To a solution of the dye (0·25 g.) in boiling acetic acid was added dropwise one of chromium trioxide (0·25 g.) in water (0·5 c.c.). The mixture was then cooled and diluted with water, and the solid collected and washed with hot water, yielding 3′-*nitro*-2-p-*nitrophenylnaphtho*(1′ : 2′-4 : 5)*triazole* (60%), m. p. 244—246° (from acetic acid) (Found: N, 20·7. $C_{16}H_9O_4N_5$ requires N, 20·9%).

Chlorination of N-*Acetyl*-3-*nitro*-2-*naphthylamine* (By A. Hardy).—The procedure for mono-chlorination was as used by Hardy and Ward.[17] Almost pure N-*acetyl*-1-*chloro*-3-*nitro*-2-*naphthylamine* was precipitated. This was collected, washed with acetic acid, and dried (0·89 g., 77%); crystallised from acetic acid it had m. p. 241° (Found: C, 54·8; H, 3·4. $C_{12}H_9O_3N_2Cl$ requires C, 54·5; H, 3·4%). Further amounts of less pure material were obtained by pouring the reaction liquors on ice. After hydrolysis of both products the combined yield of 1-*chloro*-3-*nitro*-2-*naphthylamine* was *ca.* 90%; from acetic acid this formed red needles, m. p. 135° (Found: C, 53·5; H, 3·1; Cl, 15·7. $C_{10}H_7O_2N_2Cl$ requires C, 54·0; H, 3·3; Cl, 15·9%). Chromatography of this amine on alumina in benzene gave one band only and no other products were detected on elution.

Diazotisation and subsequent deamination by the methods of Hodgson and Turner [18] gave 1-chloro-3-nitronaphthalene (65%), m. p. 130°, identified with a specimen prepared by a Sandmeyer reaction from 3-nitro-1-naphthylamine (Hodgson and Birtwell [19] give m. p. 129·5°).

Pouring the diazonium solution into water containing sodium acetate instantly precipitated in almost quantitative yield 2-*diazo*-3-*nitro*-1-*naphthol*, m. p. 187° (decomp.) (from benzene) (Found: C, 55·8; H, 2·4; N, 19·7. $C_{10}H_5O_3N$ requires C, 55·8; H, 2·3; N, 19·5%).

[17] Hardy and Ward, *J.*, 1956, 1979.
[18] Hodgson and Turner, *J.*, (*a*) 1942, 748; (*b*) 1943, 68.
[19] Hodgson and Birtwell, *J.*, 1944, 75.

When chlorination was continued for 1 hr. at 100° subsequent hydrolysis, followed by chromatography, revealed only the monochloroamine.

Bromination of 3-*Nitro*-2-*naphthylamine.*—(*a*) The amine (1 g.) in chloroform (20 c.c.) was treated with bromine (1 g., *ca.* 1·1 mol.) in chloroform (5 c.c.). After 10 hr. the precipitated hydrobromide was collected, air-dried, and on basification with aqueous ammonia yielded 1-*bromo*-3-*nitro*-2-*naphthylamine*. Chromatography of this on alumina in benzene yielded a single band and elution gave red needles, m. p. 133—134° (Found: C, 44·7; H, 2·6. $C_{10}H_7O_2N_2Br$ requires C, 45·0; H, 2·6%). Further bromo-amine was obtained by concentration of the original filtrate, making the total yield quantitative.

The bromo-amine was diazotised by the method of Hodgson and Turner,[18b] and pouring the diazo-solution into water gave an almost quantitative yield of 2-diazo-3-nitro-1-naphthol.

(*b*) The above monobromo-amine (1 g.) in chloroform (25 c.c.) was treated with bromine (2·3 g., 3 mol.) in chloroform (12 c.c.). The precipitated 1 : 6-*dibromo*-3-*nitro*-2-*naphthylamine* was collected and from benzene gave deep red needles, m. p. 186° (Found: Br, 46·3. $C_{10}H_6O_2N_2Br_2$ requires Br, 46·2%). Further dibromo-amine was obtained by concentration of the original filtrate (total yield, 88%). Direct dibromination of the 3-nitro-2-naphthylamine was less satisfactory.

Diazotisation of the dibromoamine by the Hodgson–Walker method[20] and subsequent Sandmeyer reaction yielded 1 : 2 : 6-*tribromo*-3-*nitronaphthalene* (85%), m. p. 181° (from 1 : 1 ethanol–acetone) (Found: C, 29·5; H, 1·05. $C_{10}H_4O_2NBr_3$ requires C, 29·3; H, 1·0%). This was converted into 3 : 4 : 7-*tribromo*-2-*naphthylamine* by refluxing the crude product (1 g.) with 90% hydrazine hydrate (0·5 g.) and 10% palladised charcoal (0·5 g.) in ethanol (60 c.c.) for 30 min. (cf. Dewar and Mole[21]), the amine being obtained by concentration of the cooled filtered mixture. This gave white needles (0·42 g., 46%), m. p. 167° (Found: C, 31·1; H, 1·6; Br, 63·2. $C_{10}H_6NBr_3$ requires C, 31·6; H, 1·6; Br, 63·1%). This amine was diazotised by Hodgson and Walker's method[19] and deaminated by Hodgson and Turner's method,[18a] yielding impure 1 : 2 : 6-tribromonaphthalene, m. p. 104—106° (56%). Purification of this by crystallisation and chromatography gave the pure compound, m. p. 117°, identical with a specimen prepared by a Sandmeyer reaction from 1 : 6-dibromo-2-naphthylamine (Claus and Philipson[22] give m. p. 118°).

Bromination of N-*Acetyl*-3-*nitro*-2-*naphthylamine.*—Treating the amide in acetic acid at room temperature for 24 hr. with bromine (1 mol.) gave crude *N*-acetyl-1-bromo-3-nitro-2-naphthylamine, identified by hydrolysis to the amine (*ca.* 95%). Refluxing the amide with 2 mols. of bromine in acetic acid for 24 hr. gave mainly the monobromo-amide with a little 1 : 6-dibromo-2-naphthylamine (arising by hydrolysis followed by bromination). N-*Acetyl*-1 : 6-*dibromo*-3-*nitro*-2-*naphthylamine*, prepared by treating a solution of the amine in warm acetic anhydride with a drop of sulphuric acid (*d* 1·84), had m. p. 251° (decomp.) (from acetic acid) (Found: Br, 41·0. $C_{12}H_6O_3N_2Br_2$ requires Br, 41·2%).

Nitration of 3-*Nitro*-N-*toluene*-p-*sulphonyl*-2-*naphthylamine.*—A suspension of the amide (1 g.) in acetic acid (3 c.c.) was treated with a mixture of nitric acid (*d* 1·5; 0·3 c.c., *ca.* 2·3 mols.) and acetic acid (2 c.c.), a crystal of sodium nitrite added, and the temperature raised slowly to 80°. After 15 min. at 70—80° the mixture was cooled to 0° for 30 min., and the solid collected and washed with acetic acid (1 c.c.), then with ether (2 × 3 c.c.), yielding material (84%), m. p. 210° (decomp.). 1 : 3-*Dinitro*-N-*toluene*-p-*sulphonyl*-2-*naphthylamine*, m. p. 228° (decomp.), crystallised from acetone (Found: C, 52·5; H, 3·4; S, 8·1. $C_{17}H_{13}O_6N_3S$ requires C, 52·7; H, 3·4; S, 8·3%). Repeating this experiment with 6 mols. of nitric acid and leaving the reaction mixture for 24 hr. at room temperature gave similar results. The amide was hydrolysed by dissolution in sulphuric acid (*d* 1·84) at 30° and pouring on ice, giving a quantitative yield of 1 : 3-*dinitro*-2-*naphthylamine*, orange red needles [from light petroleum (b. p. 100—120°)], m. p. 158—159° (Found: C, 51·5; H, 2·9. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0%).

N-*Acetyl*-1 : 3-*dinitro*-2-*naphthylamine* was prepared by treating the amine in acetic anhydride with a drop of sulphuric acid (*d* 1·84) and purified by extraction with cold 2N-aqueous sodium hydroxide. Subsequent acidification and crystallisation from aqueous acetic acid gave the amide, m. p. 240° (Found: C, 52·8; H, 3·2. $C_{12}H_9O_5N_3$ requires C, 52·4; H, 3·3%).

[20] Hodgson and Walker, *J.*, 1933, 1620.
[21] Dewar and Mole, *J.*, 1956, 2556.
[22] Claus and Philipson, *J. prakt. Chem.*, 1891, **43**, 47.

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The 1 : 3-dinitro-2-naphthylamine was diazotised by Hodgson and Turner's method.[18b] Pouring the diazonium solution into water gave a quantitative yield of 2-diazo-3-nitro-1-naphthol. Attempts to convert this into 3-nitro-1-naphthol by the methods of Hodgson and Turner,[23] or Hodgson and Birtwell,[24] failed, the former yielding largely unchanged starting material.

Nitration of 3-*Nitro*-N-*phthaloyl*-2-*naphthylamine.*—The amide (2 g.) was stirred gradually into nitric acid (*d* 1·5; 7 c.c.) during 10 min. below −5°. After 30 min. more the mixture was poured on ice (50 g.), and the solid collected and washed well with water (the yield calc. for mononitration was quantitative) (Found: N, 11·5. Calc. for $C_{16}H_7O_4N_3$: N, 11·6%). The crude phthalimide was hydrolysed by refluxing with aqueous-ethanolic hydrazine hydrate (cf. Hardy and Ward [8]), the dried crude product so obtained was extracted with warm 9 : 1 v/v benzene–ethyl acetate, and the mixed amines were separated by chromatography.[25] 3 : 8-*Dinitro*-2-*naphthylamine* had m. p. 239—241° (Found: C, 51·3; H, 3·0. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0%) and 3 : 5-*dinitro*-2-*naphthylamine* m. p. 228—230° (Found: C, 51·1; H, 3·0%).

N-*Acetyl*-3 : 5-, m. p. 249° (Found: C, 52·4; H, 3·9. $C_{12}H_9O_5N_3$ requires C, 52·4; H, 3·3), and -3 : 8-*dinitro*-2-*naphthylamine*, m. p. 204° (Found: C, 52·2; H, 3·5%), were prepared.

The amines were diazotised and deaminated as by Hodgson and Turner,[18] 3 : 5-dinitro-2-naphthylamine giving 1 : 7-dinitronaphthalene (21%), and 3 : 8-dinitro-2-naphthylamine giving 1 : 6-dinitronaphthalene (38%), identical with authentic specimens.

1 : 6 : 7-*Trinitronaphthalene.*—This was prepared directly from the mixed 3 : 5- and 3 : 8-dinitro-2-naphthylamines.[8,9] The crude dry product from 0·2 g. was extracted by boiling chloroform (charcoal), and the filtered extract concentrated to 10 c.c. to afford 1 : 6 : 7-*trinitronaphthalene* (0·07 g., 31%), m. p. 196—199° (Found: C, 45·6; H, 2·0; N, 15·7. $C_{10}H_5O_6N_3$ requires C, 45·6; H, 1·9; N, 16·0%).

Nitration of N-*Acetyl*-3-*nitro*-2-*naphthylamine.*—(*a*) The amide (1 g.), suspended in acetic acid (10 c.c.), was treated with a mixture of nitric acid (*d* 1·5; 0·5 g., 1·8 mols.), boron trifluoride–acetic acid complex (40% w/w; 4 g.), and acetic acid (15 c.c.). A crystal of sodium nitrite was added, and the temperature raised to 75° during 20 min. and then kept at 60—65° for 5 min. The mixture was added to ice-water (500 g.), and the solid collected, washed with water, and dried at 50° in a vacuum (yield 1 g., 85%) (Found: N, 15·1. $C_{12}H_8O_5N_3$ requires N, 15·3%). The product was hydrolysed for 2 hr. with a refluxing mixture of ethanol (12 c.c.) and aqueous sulphuric (1 : 1 v/v; 8 c.c.). Pouring the whole on ice and basification gave an almost quantitative yield of mixed dinitronaphthylamines (Found: C, 51·7; H, 2·8; N, 17·9. Calc. for $C_{10}H_7O_4N_3$: C, 51·5; H, 3·0; N, 18·0%). Chromatography of the mixture [25] yielded pure 1 : 3-dinitro-2-naphthylamine, 3 : 8-dinitro-2-naphthylamine, and 3 : 6-*dinitro*-2-*naphthylamine*, m. p. 239—240° (Found: C, 50·9; H, 3·1%).

3 : 6-Dinitro-2-naphthylamine, by diazotisation and deamination,[18] gave 2 : 7-dinitronaphthalene (53%), identical with an authentic specimen.

(*b*) The amide (1 g.) was added gradually to nitric acid (*d* 1·5; 6 c.c.) below −5°, and kept at −5° to −10° for 90 min. with stirring. The mixture was poured into ice-water (50 g.), and the solid collected, washed with water, and dried *in vacuo* at 55° (yield 1 g., 72%). After hydrolysis (as above) and pouring into ice-water a quantitative yield of mixed trinitronaphthylamines was obtained. Chromatography [25] afforded 1 : 3 : 8-*trinitro*-2-*naphthylamine*, m. p. 268—270° (decomp.) (Found: C, 42·8; H, 2·1; N, 19·9. $C_{10}H_6O_6N_4$ requires C, 43·2; H, 2·2; N, 20·2%) and 1 : 3 : 5-*trinitro*-2-*naphthylamine* (after rechromatography, m. p. 181—183°) (Found: C, 43·0; H, 2·2; N, 19·8%).

Diazo-naphthols were obtained from these amines by diazotisation [18a] and pouring of the diazonium solutions into water. 1-*Diazo*-3 : 5-*dinitro*-2-*naphthol* had m. p. 128—130° (decomp.) (from aqueous ethanol) (Found: C, 46·2; H, 1·5; N, 22·0. $C_{10}H_4O_5N_4$ requires C, 46·2; H, 1·5; N, 21·5%). 1-*Diazo*-3 : 8-*dinitro*-2-*naphthol* had m. p. 220° (decomp.) (from acetone) (Found: 46·2; H, 1·5; N, 21·7%).

Nitration of 3-*Nitro*-N-m-*nitrobenzenesulphonyl*-2-*naphthylamine.*—(*a*) The amide (1 g.) in acetic acid (15 c.c.) at 50° was treated (dropwise) with nitric acid (*d* 1·5; 1 c.c., *ca.* 7 mols.), and the temperature raised to 80° and kept thereat for 15 min. The mixture was then set aside for 1 hr., and the solid collected and washed with acetic acid (1·5 c.c.) and then ether (3 × 8 c.c.) (yield 0·7 g., 62%). The product was hydrolysed by dissolution in sulphuric acid (*d* 1·84;

[23] Hodgson and Turner, *J.*, 1944, 8.
[24] Hodgson and Birtwell, *J.*, 1943, 86.
[25] Ward and Wells, *J.*, 1957, 2836.

40 c.c.) at 50°, storage overnight, and pouring on ice. Purification by chromatography gave pure 1 : 3-dinitro-2-naphthylamine.

(*b*) The amide (1 g.) was added slowly with stirring to nitric acid (*d* 1·5; 2 c.c.) at 20° and the solution set aside for 1 hr. Acetic acid (3·5 c.c.) was added and after 40 hr. the solid was collected, washed with acetic acid (3 c.c.), then ether (6 c.c.), and dried *in vacuo* at 20° (0·72 g., 60%) (Found: C, 40·8; H, 1·92; N, 14·1. $C_{16}H_9O_{10}N_5S$ requires C, 41·5; H, 1·96; N, 15·5%). Further material was obtained by pouring the original filtrate on ice. After hydrolysis, as above, both products afforded a red amine which was further purified by chromatography (single band only), giving 1 : 3 : 6-*trinitro-2-naphthylamine*, m. p. 140—142° (Found: C, 42·1; H, 2·2. $C_{10}H_6O_6N_4$ requires C, 43·2; H, 2·2%).

Further Nitration of N-Acetyl-dinitro-2-naphthylamines.—(*a*) The procedure was as employed for the dinitration of *N*-acetyl-3-nitro-2-naphthylamine, the yields (calc. for mononitration) were almost quantitative. *N*-Acetyl-3 : 5-dinitro-2-naphthylamine gave [after hydrolysis, purification by chromatography, and crystallisation from light petroleum (b. p. 100—120°)] 1 : 3 : 5-trinitro-2-naphthylamine, and *N*-acetyl-3 : 8-dinitro-2-naphthylamine similarly gave 1 : 3 : 8-trinitro-2-naphthylamine, these being identical with the amines obtained by dinitration of *N*-acetyl-3-nitro-2-naphthylamine. *N*-Acetyl-1 : 3-dinitro-2-naphthylamine was recovered unchanged.

(*b*) *N*-Acetyl-3 : 5- and -3 : 8-dinitro-2-naphthylamine were recovered unchanged when treated by the procedure employed for mononitrating *N*-acetyl-3-nitro-2-naphthylamine.

Nitration of N-Acetyl-3-chloro-1-naphthylamine (with A. Hardy).—The amide (0·1 g.) was added to nitric acid (*d* 1·42) during 5 min., then heated on the steam-bath for 15 min. After cooling, the solution was poured into water, and the solid collected, washed with water, and dried (0·083 g.). This was chromatographed in benzene on alumina, elution being with benzene–ethyl acetate. Four bands were obtained but the main yellow one gave white needles of an *N-acetyl-chlorodinitronaphthylamine* (0·055 g.), m. p. 275° (from acetic acid) (Hodgson and Elliott [15] give the m. p. of their supposed *N*-acetyl-2 : 3-dinitro-1-naphthylamine as 275·5°) (Found: C, 46·8; H, 2·9; Cl, 11·4. $C_{12}H_8O_5N_3Cl$ requires C, 46·6; H, 2·9; Cl, 11·4%).

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972. *Spasmolytics Derived from Xanthen.*

By A. A. Goldberg and A. H. Wragg.

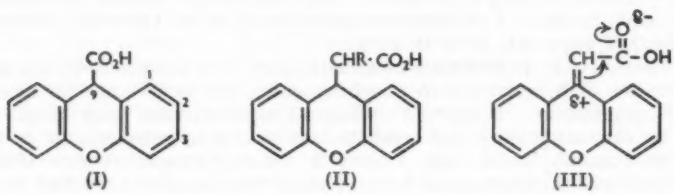
9-Xanthenyl-acetic and -glycollic and 9-xanthenylideneacetic acid have been synthesised and converted into their 2-dialkylaminoalkyl esters. These, together with their ethobromides, have been examined for antispasmodic activity by the Magnus method.

Because of the high antispasmodic activity of the methobromides of 2-dialkylaminoethyl esters [1] of xanthen-9-carboxylic acid (I), attention was directed to analogous esters in which the distance between the carbonyl group and the $C_{(9)}$-atom was greater. The current theory of antispasmodic action is that the acetylcholine-sensitive receptor surfaces of parasympathetically innervated organs can only be effectively blockaded by a compound which has two foci for attachment to the surface. One of these foci is a terminal tertiary or quaternary nitrogen atom and the other, which must be between 5 and 10 Å distant from the nitrogen head,[2] may be one of a number of, as yet, ill-defined groupings to which is attached one or more groups large enough to constitute a protective shield over the receptors and prevent access to them of the natural spasmogenic neurohormone. From the structure of the most widely used antispasmodics it appears that the unsaturation electrons

[1] Burtner and Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 1582.
[2] Lands and Luduena, *J. Pharm. Exp. Therap.*, 1956, **117**, 331.

XUM

of a polarised carbonyl or ethylene group, or a lone pair on a hydroxyl oxygen or a second nitrogen atom constitutes the second focus for attachment to the reception surface. The value of the xanthenyl group as the shielding structure may be related, not only to its size, but to its ability to tolerate a positive charge because of high resonance stability of the resulting cation; this allows a further supply of electrons to be available at the group attached to the 9-position which may assist the compound to become fastened to the receptors.



(I) (II) (III)

Accordingly the dialkylaminoethyl esters of 9-xanthenyl-acetic (II; R = H) and -glycollic acids (II; R = OH) have been synthesised and converted into their ethobromides. The distance between the $C_{(9)}$-atom and the carbonyl-carbon atom in these compounds is 1·54 Å greater than in esters of xanthen-9-carboxylic acid. 9-Xanthenylideneacetic acid (III) has also been synthesised and converted into its dialkylaminoethyl ester and the ester ethobromide. In these the $C_{(9)}$–C(O) distance is 1·34 Å greater than in esters of xanthen-9-carboxylic acid and the carbonyl-oxygen atom is very strongly polarised by the mesomeric drift shown; in addition, the molecule has a degree of rigidity because of the double bond. Since this work was completed (B.P. Appl. 9502—4/1956), McConnel *et al.* have reported esters of 9-xanthenylacetic acid but not their activities.

Condensation of 9-hydroxyxanthen with malonic acid in cold acetic acid gave 9-xanthenylmalonic acid which, when heated with pyridine, yielded 9-xanthenylacetic acid (overall yield 86%). This procedure is preferable to that of Fosse [4] since the considerable disproportionation of 9-hydroxyxanthen to xanthone and xanthen is avoided. 3-Chloro-9-hydroxyxanthen by the same method yielded 3-chloro-9-xanthenylacetic acid.

With tartronic acid 9-hydroxyxanthen gave 9-xanthenyltartronic acid but the most favourable yield was 21%, this being reduced by the addition of protonising agents or the use of different solvents. Decarboxylation gave a theoretical yield of 9-xanthenylglycollic acid. To improve the yield and avoid the relatively inaccessible tartronic acid, attempts were made to brominate 9-xanthenylacetic acid in the α-position and obtain xanthenylglycollic acid from the product by hydrolysis. Unfortunately bromination is effected more readily in the nucleus than in the side chain. Bromomalonic acid, however, condensed with 9-hydroxyxanthen to give a red oil from which α-bromo-α-9-xanthenylmalonic acid could not be isolated; on thermal decarboxylation the oil gave α-bromo-α-9-xanthenylacetic acid.

Treatment of the last-mentioned acid with hot concentrated aqueous sodium hydroxide eliminated hydrogen bromide quantitatively, with production of 9-xanthenylideneacetic acid. With water buffered at pH 8, the bromo-acid gave 9-xanthenylglycollic acid and 9-methylenexanthen in 75% and 25% yield respectively; these were easily separable because of the volatility of the latter in steam. This method constitutes a very convenient route to 9-xanthenylglycollic acid. Substantially the same results were obtained at pH 4·5 and 3·0, but at pH 1·3 only 9-methylenexanthen was formed. 9-Xanthenylglycollic acid is stable at all pH values in water at 100°; 9-xanthenylideneacetic acid is stable at high pH but decomposes at low pH without giving 9-methylenexanthen. The production

[3] McConnell, Petrow, and Sturgeon, *J.*, 1956, 812.
[4] Fosse, *Compt. rend.*, 1906, **143**, 749; *Ann. Chim.* (*France*), 1916, **6**, 31; *Bull. Soc. chim. France*, 1908, **35**, 1007.

of the methylenexanthen therefore appears to be by direct formation from the bromo-acid by simultaneous elimination of hydrogen bromide and carbon dioxide.

Fosse [4] represents the reaction of 9-hydroxyxanthen with a reactive methylene group as a type of Perkin reaction but it appears much more likely to be an alkylation of a carbanion by the xanthenyl cation. As the series benzyl alcohol, diphenylmethanol, triphenylmethanol, 9-hydroxyxanthen is ascended there is increasing tendency for ionisation (with fission of hydroxyl ion) because of increasing resonance stabilisation [5] of the residual cation. Alkylation of the methylene group in malonic esters and acids is normally a base-catalysed reaction; it appears that in a weakly acid (acetic) or weakly basic (pyridine) solvent ionisation of both 9-hydroxyxanthen and the methylene compound is sufficiently pronounced to allow reaction to proceed.

9-Xanthenylideneacetic acid is an exceptionally weak acid, (pK_a 7·4). This is understandable since the carbonyl $-M$ mechanism indicated in (III) will be strongly augmented by the xanthenyl nucleus which can easily tolerate a positive charge.[5]

Conversion of the acids into their dialkylaminoalkyl esters proceeded easily by the Horenstein–Pählicke [6] procedure; quaternisation was carried out in ether or benzene solution.

Spasmolytic Activities [with M. S. Shapero]

The spasmolytic activities of the esters and quaternary salts against acetylcholine bromide, histamine, nicotine, and serotonin spasm of isolated guinea-pig ileum were determined by the Magnus method and are recorded in the Table. The spasmogen dilution

Spasmolytic activities of esters YOX *and amides* YX *of the acids* HOX (I—III).

Y	Acetylcholine bromide p*D* 7·08 *	Histamine p*D* 7·08 *	Nicotine p*D* 5·34 *	Serotonin p*D* 5·78 *
Acid (I)				
·O·C_2H_4·NEt_2	7·95 (0·04)	6·23 (0·07)	6·80 (0·03)	7·2 (0·18)
·O·C_2H_4·NEt_2,HBr	8·80 (0·12)	5·40 (0·10)	7·08 (0·05)	8·2 (0·07)
·O·C_2H_4·$NEt_2Me^+Br^-$	8·52 (0·03)	5·34 (0·04)	7·98 (0·04)	8·36 (0·04)
·O·C_2H_4·NPr_2	8·09 (0·02)	5·74 (0·03)	6·32 (0·65)	7·5 (0·21)
·O·C_2H_4·$NPr_2Me^+Br^-$	9·11 (0·07)	5·54 (0·05)	6·38 (0·04)	8·92 (0·08)
Acid (II; R = H)				
·O·C_2H_4·NEt_2	6·00 (0·02)	5·79 (0·10)	6·24 (0·06)	6·27 (0·12)
·O·C_2H_4·NEt_2,HBr	7·24 (0·24)	4·51 (0·04)	6·90 (0·15)	7·07 (0·06)
·NH·C_2H_4·NEt_2	4·62 (0·05)	4·97 (0·03)	5·27 (0·08)	5·3 (0·05)
·NH·C_2H_4·NEt_2,HBr	5·40 (0·05)	3·82 (0·02)	5·51 (0·09)	4·65 (0·12)
·NH·C_2H_4·NEt_2	4·61 (0·07)	5·39 (0·05)	5·74 (0·12)	5·6 (0·09)
·NH·C_2H_4·NEt_2,HBr	5·04 (0·05)	3·95 (0·04)	5·76 (0·10)	5·1 (0·09)
Acid (II; R = OH)				
·O·C_2H_4·NEt_2	5·60 (0·01)	5·0 (0·06)	5·95 (0·11)	5·17 (0·04)
·O·C_2H_4·NEt_2,HBr	5·79 (0·03)	4·41 (0·04)	5·69 (0·06)	5·67 (0·05)
Acid (III)				
·O·C_2H_4·NEt_2	5·13 (0·05)	5·17 (0·04)	5·85 (0·09)	5·74 (0·07)
·O·C_2H_4·NEt_2,HBr	5·70 (0·09)	4·62 (0·07)	6·30 (0·12)	6·00 (0·18)
3-Chloro-derivative of acid (II; R = H)				
·O·C_2H_4·NEt_2	5·67 (0·01)	5·47 (0·06)	6·35 (0·12)	5·68 (0·06)
·O·C_2H_4·NEt_2,HBr	6·89 (0·02)	5·03 (0·05)	6·26 (0·11)	6·00 (0·08)
Atropine	8·85 (0·19)	5·53 (0·08)	7·77 (0·16)	7·17 (0·24)
Papaverine	5·04 (0·03)	5·41 (0·05)	5·40 (0·20)	5·10 (0·17)
Chloropropromazine	5·67 (0·07)	7·89 (0·09)	5·70 (0·10)	6·25 (0·06)

* p*D* of spasmogen in bath.

(p*D*) given at the head of each column produced *ca.* 40% reduction of the normal length of the ileum strip in all cases. The activities of the spasmolytic agents are recorded as the dilution potential (p*D*) which effects 50% release of the spasm; the figures are the means

[5] Shriner in "Roger Adams Symposium," Sept. 1954 (Chapman Hall), p. 103.
[6] Horenstein and Pählicke, *Ber.*, 1938, **71**, 1644.

from 6 strips with the standard deviations in parentheses. Dilutions are given on the p*D* scale; p*D* *x* means 1 part of spasmolytic in 10^x parts of solution.

The following observations can be made from the tabulated results: (i) In all the compounds quaternisation of the terminal nitrogen atom strongly increases activity against acetylcholine, nicotine, and serotonin but substantially reduces activity against histamine spasm. (ii) Increasing the $C_{(9)}$–C(O) distance effects a pronounced decrease in activity against acetylcholine, histamine, and serotonin, and a definite, although smaller, decrease against nicotine spasm. (iii) Surprisingly, introducing an α-hydroxyl group into the xanthenylacetic ester considerably reduces activity against acetylcholine and serotonin and, to a smaller extent, against histamine and serotonin. (iv) The 9 : α-double bond reduces activities below those of the saturated compounds. (v) The amides are much less active than the corresponding esters.

Experimental

9-Hydroxyxanthen.—The following method is less hazardous and more suitable for large quantities than that recorded in *Org. Synth.*[7] A suspension of finely ground xanthone (50 g.) in 95% alcohol (550 c.c.) was refluxed on the water-bath over 3½% sodium amalgam (600 g.) for 1 hr.; the xanthone dissolved in *ca.* 20 min. The supernatant solution was decanted, filtered, and poured into stirred ice-water (4 l.). The 9-hydroxyxanthen was immediately precipitated. Carbon dioxide was passed in until the liquor was neutral, the colourless precipitate collected, washed with cold water, and dried at 10 mm. over potassium hydroxide for 2 days, then over phosphoric oxide for 2 days, and stored in a tight bottle away from light. The yield was 44 g., and the m. p. 124—126°. Samples thus kept for 2 years were substantially unchanged (contrast Ward [8]) as shown by acetone-solubility and preparation of derivatives. 9-Hydroxyxanthen is very soluble in cold acetone (1 g./10 c.c.); xanthone is almost insoluble.

A sample (4·0 g.) was dissolved in glacial acetic acid (10 c.c.) and added to a solution of toluene-*p*-sulphinic acid (3·2 g.) in hot acetic acid (10 c.c.); a crystalline precipitate rapidly separated. In the morning the mixture was poured into water (100 c.c.), and the precipitate collected and crystallised from acetic acid; *9-toluene-*p*-sulphonylxanthen* (5·2 g., 77%) was obtained in pink needles, m. p. 206—208° (Found: C, 71·1; H, 4·8; S, 9·3. $C_{20}H_{16}O_3S$ requires C, 71·5; H, 4·8; S, 9·5%).

9-Xanthenylacetic Acid.—A solution of malonic acid (20 g.) in glacial acetic acid (200 c.c.) was added to one of 9-hydroxyxanthen (40 g.) in acetic acid (100 c.c.). The mixture was kept at room temperature overnight, then poured into stirred ice-water (1200 c.c.), the precipitate collected and extracted with hot aqueous sodium carbonate, and the 9-xanthenylmalonic acid (52 g., 87%; m. p. 120—130°) precipitated by acidification, collected, washed with water, and dried at 40°. A sample crystallised from aqueous methanol in very pale green needles, m. p. 150—152° after dehydration at 100° (Found: C, 68·0; H, 4·4. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%).

The crude 9-xanthenylmalonic acid (50 g.) was refluxed with pyridine (125 c.c.) for ½ hr. and the solution was cooled and poured into stirred 5N-hydrochloric acid (625 c.c.). The precipitate was collected, washed, and stirred with dilute aqueous ammonia, and the insoluble material removed; acidification gave 9-xanthenylacetic acid (43 g., m. p. 150—152°). A sample crystallised from aqueous alcohol in colourless needles, m. p. 154—156° [Found: *M* (by titration), 243; C, 74·7; H, 5·0%. Calc. for $C_{15}H_{12}O_3$: *M*, 240; C, 75·0; H, 5·0%)]. The acid has pK_a 6·6 (xanthen-9-carboxylic acid has pK_a 5·9).

The *chloride*, prepared by refluxing the acid (12 g.) with thionyl chloride (10 c.c.) in benzene (100 c.c.) for 2 hr. and then distilling off the solvent, was obtained in greenish needles (from benzene), m. p. 98° (Found: Cl, 13·7. $C_{15}H_{11}O_2Cl$ requires Cl, 13·7%). This yielded the following colourless derivatives as needles: *amide* (from benzene), m. p. 194° (Found: C, 75·6; H, 5·3; N, 5·7. $C_{15}H_{13}O_2N$ requires C, 75·4; H, 5·4; N, 5·8%); *anilide* (from alcohol), m. p. 220° (Found: C, 79·7; H, 5·2; N, 4·5. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4; N, 4·5%); p-*chloroanilide* (from benzene), m. p. 225° (Found: N, 4·0; Cl, 10·0. $C_{21}H_{16}O_2NCl$ requires N, 4·0; Cl, 10·2%).

[7] *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 554.
[8] Ward quoted in Ref. 7, p. 555.

9-Xanthenylacetic acid is recovered in nearly theoretical yield after 1 hour's boiling with excess of 5N-hydrochloric acid or 5N-sodium hydroxide. It is rapidly decomposed by sulphuric acid at 100°.

Bromination of 9-Xanthenylacetic Acid.—(*a*) The acid (5 g.) was heated in acetic acid (45 c.c.) with bromine (3·83 g.) at 80° for 1 hr. The solution was poured into water and extracted with ether (2 × 50 c.c.), and the combined ethereal solutions were extracted with N-sodium hydroxide (2 × 30 c.c.). The alkaline extract gradually deposited a sodium salt (1·2 g.) which gave an acid, m. p. 192°, which must be a (nuclear)*dibromo-9-xanthenylacetic acid* since there was no release of bromide ion in boiling alkali [Found: *M* (by titration), 408; Br, 40·3%. $C_{15}H_{10}O_3Br_2$ requires *M*, 398; Br, 40·2%].

(*b*) The unbrominated acid (2·4 g.; 0·01 mol.) was refluxed with thionyl chloride (10 c.c.) for 2 hr., then bromine (0·53 c.c.) in thionyl chloride (7·5 c.c.) was added. After 1 hr. the solution was poured on ice (40 g.) and left for 2 days. The green precipitate was collected, shaken overnight with 20% aqueous sodium carbonate (25 c.c.), and the mixture filtered and acidified. A (nuclear)*monobromo-9-xanthenylacetic acid* (0·9 g.), m. p. 160—162°, was precipitated (Found: *M*, 312; Br, 24·7%. $C_{15}H_{10}O_3Br$ requires *M*, 319; Br, 25·1%).

α-Bromo-α-9-xanthenylacetic Acid.—Solutions of bromomalonic acid (40 g.) in warm acetic acid (160 c.c.) and 9-hydroxyxanthen (40 g.) in the same solvent (200 c.c.) were mixed and kept at room temperature for 190 hr. Water (400 c.c.) and saturated aqueous sodium chloride (60 c.c.) were added, and the small precipitate (A) was collected. The filtrate was evaporated to *ca.* 300 c.c. at 10 mm., and the mixture diluted with water (300 c.c.), again evaporated to *ca.* 300 c.c., and made alkaline with sodium carbonate. The precipitate (A) was added, and the mixture filtered, chilled, and shaken with ether for 10 min. during which hydrochloric acid was added until the pH was 2. The ethereal extract was washed with water (150 c.c.), dried (Na_2SO_4), and evaporated. The remaining red oil (crude malonic acid) was refluxed in toluene (400 c.c.) and benzene (100 c.c.) for 3 hr. Next morning the mixture was extracted with saturated potassium hydrogen carbonate solution (3 × 80 c.c.), and the aqueous extract washed with ether, chilled, acidified with hydrochloric acid, and extracted with ether (2 × 80 c.c.). The dried ethereal solution was evaporated, the remaining oil ground with ligroin (b. p. 40—60°) until it crystallised, and the solid drained and washed with a little cold toluene. Crystallisation from ligroin (b. p. 100—120°) gave *α-bromo-α-9-xanthenylacetic acid* (19 g.) in colourless prisms, m. p. 148—150° (Found: *M*, 322; Br, 25·2%. $C_{15}H_{11}O_3Br$ requires *M*, 319; Br, 25·1%). The acid has pK_a 3·9. Treatment of this acid (1·0 g.) in acetic acid (75 c.c.) with chromic acid (5 g.) for 15 min. gave a 55% yield of xanthone.

9-Xanthenyltartronic Acid.—A solution of tartronic acid [9] (36 g.) in warm glacial acetic acid (140 c.c.) was added to one of 9-hydroxyxanthen (60 g.) in the same solvent (200 c.c.). The solution was kept at room temperature for 72 hr., then poured into ice-water (1200 c.c.), the precipitate collected, and the filtrate (B) kept. The precipitate was extracted with a slight excess of 2N-aqueous ammonia, and the extract added to the above filtrate (B). The combined solution (which was still acid) was extracted with ether (2 × 300 c.c.), and the ethereal solution re-extracted with 2N-ammonia (3 × 50 c.c.). The aqueous alkaline solution was acidified with hydrochloric acid, and the precipitate collected; crystallisation from water gave *9-xanthenyltartronic acid* as colourless needles (20 g.), m. p. 174° (decomp.) (Found: C, 63·7; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%).

9-Xanthenylglycollic Acid.—A solution of the foregoing acid (20 g.) in pyridine (80 c.c.) was refluxed for 30 min., cooled, and poured into 5N-hydrochloric acid (350 c.c.) at 5° and the crystalline *9-xanthenylglycollic acid* (15 g.), m. p. 224—226°, collected (Found: C, 70·1; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The acid has pK_a 4·7.

9-Xanthenylideneacetic Acid.—A solution of α-bromo-α-9-xanthenylacetic acid (20 g.) in 2N-sodium hydroxide (380 c.c.) was refluxed for 2½ hr. In the morning a little water was added to dissolve the small precipitate, the filtered solution adjusted to pH 2 with hydrochloric acid, and the solution extracted with ether (3 × 300 c.c.). The ethereal solution was washed with water (50 c.c.) and dried (Na_2SO_4), and the ether removed, first at atmospheric and then at reduced pressure. Benzene (500 c.c.) was added and some distilled off at reduced pressure to remove traces of water; the residual solution (250 c.c.) was diluted with ligroin (b. p. 40—60°), and the precipitated *9-xanthenylideneacetic acid* (13·1 g.; m. p. 122—126°) collected. Crystallisation from benzene–ligroin gave the pure compound (12·2 g., 82%) as pale yellow needles,

[9] Bak, *Annalen*, 1938, **337**, 286.

XUM

m. p. 142° (Found: C, 75·5; H, 4·2. $C_{15}H_{10}O_3$ requires C, 75·7; H, 4·2%). The acid has pK_a 7·4.

Hydrolysis of α-Bromo-α-9-xanthenylacetic Acid.—(i) *At* pH 7·0. A solution of the acid (10·6 g.), disodium hydrogen phosphate dodecahydrate (35·8 g.), and potassium dihydrogen phosphate (9·1 g.) in water (110 c.c.) and dioxan (85 c.c.) was refluxed for 25 hr. The solvent was removed at reduced pressure and the residue lixiviated with aqueous sodium carbonate. The insoluble methylenexanthen was filtered off, the solution acidified with dilute nitric acid, and the precipitated **9-*xanthenylglycollic acid*** (6·5 g.; m. p. 220°) collected. This crystallised from ethyl acetate–toluene in colourless needles (5·7 g., 67%), m. p. and mixed m. p. 225° (Found: *M*, 257; C, 70·1; H, 4·6%. $C_{15}H_{12}O_4$ requires *M*, 256; C, 70·3; H, 4·7%).

The crude **9-*methylenexanthen*** was distilled in a current of steam and obtained in lustrous colourless plates (1·5 g., 23%), m. p. 112° (Found: C, 86·4; H, 5·2. $C_{14}H_{10}O$ requires C, 86·6; H, 5·2%). 9-Methylenexanthen is unchanged at the b. p. by 2N-hydrochloric acid or 5N-sodium hydroxide for 24 hr.

(ii) *At* pH 4. A solution of the acid (10·6 g.), sodium formate (18·1 g.), and formic acid (6·4 c.c.) in water (120 c.c.) and dioxan (85 c.c.) was refluxed for 24 hr. In the same manner there were obtained 9-xanthenylglycollic acid (4·9 g., 58%), m. p. and mixed m. p. 225°, and methylenexanthen (1·0 g., 15%), m. p. 112°.

When the sodium formate and formic acid were replaced by sodium acetate (10·3 g.) and acetic acid (1·8 c.c.) (pH 4·7) there were obtained 3·9 g. (49%) of the glycollic acid, m. p. 225°, and 2 g. (33%) of methylenexanthen, m. p. 112°.

(iii) *At* pH 7—2. A solution of the acid (10·6 g.) and potassium carbonate (2·25 g., 1 equiv.) in water (300 c.c.) was refluxed for 30 min. The solution rapidly became cloudy and an oil was precipitated, the pH falling from 7·0 to 2·0. There were obtained 2·9 g. (34%) of glycollic acid and 4·0 g. (63%) of methylenexanthen.

(iv) *At* pH 1·5—1·0. A solution of the acid (10·6 g.) in water (140 c.c.) and dioxan (85 c.c.) was refluxed for 24 hr., giving 0·7 g. (11%) of methylenexanthen, m. p. 112°, and 7·3 g. of an intractable mixture of 9-xanthenylglycollic acid and unchanged starting material.

3-Chloro-9-hydroxyxanthen.—A suspension of finely divided 3-chloroxanthone (25 g.) in 95% ethanol (300 c.c.) was refluxed for 2 hr. over 3½% sodium amalgam (300 g.), the solid dissolving. The filtered solution was poured with stirring into ice-water (2 l.), the suspension neutralised with carbon dioxide, and the colourless precipitate of ***3-chloro-9-hydroxyxanthen*** (23·1 g., 92%), m. p. 175—177°, collected, washed with water, and dried *in vacuo* (Found: Cl, 14·8. $C_{13}H_9O_2Cl$ requires Cl, 15·3%). The material cannot be purified by crystallisation. The following derivatives were made by adding a warm saturated solution of the alcohol in acetic acid to a hot solution of benzamide or toluene-*p*-sulphonamide in the same solvent; the derivatives separated overnight almost quantitatively in colourless needles and were recrystallised from alcohol–pyridine: **9-*Benzamido*-3-*chloro*-**, m. p. 234—236° (Found: N, 4·3; Cl, 10·7. $C_{20}H_{14}O_2NCl$ requires N, 4·2; Cl, 10·6%), and **3-*chloro*-9-*toluene*-p-*sulphonamido*-*xanthen***, m. p. 172—174° (Found: N, 3·7; Cl, 9·1; S, 8·2. $C_{20}H_{16}O_3NSCl$ requires N, 3·6; Cl, 9·2; S, 8·3%).

3-Chloro-9-xanthenylmalonic Acid.—3-Chloro-9-hydroxyxanthen (16·7 g.) and malonic acid (7·2 g.) were kept in acetic acid (80 c.c.) for 96 hr. at room temperature, the mixture was poured into water (250 c.c.), the precipitated oil (C), which partially solidified, was collected, and the filtrate extracted with ether (2 × 100 c.c.). The ethereal solution was extracted with 4N-ammonia (2 × 150 c.c.), the extracts were combined with the solid (C), and the insoluble non-acidic material was removed. Acidification of the filtrate precipitated ***3-chloro-9-xanthenylmalonic acid*** as a buff powder (17 g.; m. p. 140—144°); this was collected, washed, and dried *in vacuo*. A sample separated from aqueous methanol as a pale brown-green powder, m. p. 166—168° (decomp.) (Found: equiv., 161; Cl, 11·0%. $C_{16}H_{11}O_5Cl$ requires equiv., 159; Cl, 11·1%).

3-Chloro-9-xanthenylacetic acid.—A solution of the foregoing crude acid (25 g.) in pyridine (75 c.c.) was refluxed for ½ hr., chilled, and poured into stirred 5N-hydrochloric acid (300 c.c.). The precipitate was separated and stirred with excess of dilute aqueous sodium carbonate, the insoluble material removed, and the filtrate acidified with dilute hydrochloric acid. ***3-Chloro-9-xanthenylacetic acid*** (18 g., 83%) was obtained as a buff solid; a sample separated from aqueous methanol in colourless rhombs, m. p. 118—120° (Found: *M*, 278; Cl, 13·1%. $C_{15}H_{11}O_3Cl$ requires *M*, 274·5; Cl, 12·9%).

2-Diethylaminoethyl 3-Chloro-9-xanthenylacetate.—3-Chloro-9-xanthenylacetic acid (6 g.), 2-diethylaminoethyl chloride (4·5 g.), and anhydrous potassium carbonate (3·1 g.) were

refluxed with dry chloroform (100 c.c.) for 24 hr. The chloroform solution was washed with 2N-sodium carbonate (50 c.c.) and then with water (2 × 50 c.c.) and dried (K_2CO_3) and the chloroform distilled off; the ester remained as a pale yellow oil. It was dissolved in the minimum of boiling alcohol and added to a concentrated hot solution of oxalic acid dihydrate (1 mol.) in alcohol; the *ester hydrogen oxalate* separated in colourless plates (5·4 g.) [Found: *M* (by titration with $HClO_4$), 467; N, 3·1; Cl 7·6%. $C_{23}H_{24}O_7NCl$ requires *M*, 463·5; N, 3·0; Cl, 7·7%]. The following were prepared in the same manner, the yields in all cases being *ca.* 80%.

2-*Diethylaminoethyl* 9-*xanthenylideneacetate hydrogen oxalate*, needles (from alcohol), m. p. 172—174° (Found: C, 64·8; H, 6·3; N, 3·3. $C_{23}H_{25}O_7N$ requires C, 64·7; H, 5·9; N, 3·3%).

2-*Diethylaminoethyl* 9-*xanthenylglycollate hydrogen oxalate*, needles (from alcohol) containing 1EtOH of crystallisation (Found: *M*, 491; N, 2·9%. $C_{23}H_{27}O_8N,C_2H_5{\cdot}OH$ requires *M*, 491; N, 2·9%).

2-*Diethylaminoethyl* 9-*xanthenylacetate hydrogen oxalate*, leaves (from alcohol), m. p. 132° (Found: *M*, 429; C, 64·0; H, 6·3; N, 3·4%. $C_{23}H_{27}O_7N$ requires *M*, 429; C, 64·3; H, 6·3; N, 3·3%). The *hydrochloride* of the base separated from benzene in colourless leaves, m. p. 146—148° (Found: N, 4·0; Cl, 9·8. $C_{21}H_{26}O_3NCl$ requires N, 3·7; Cl, 9·5%).

2-*Diethylaminoethyl xanthen*-9-*carboxylate hydrogen oxalate*, needles (from alcohol) (Found: *M*, 412. $C_{22}H_{25}O_7N$ requires *M*, 415).

2-*Diisopropylaminoethyl xanthen*-9-*carboxylate*, an oil which slowly solidified (Found: *M*, 351; N, 4·0%. $C_{22}H_{27}O_3N$ requires *M*, 353; N, 4·0%).

2-*Diethylaminoethyl* 3-*Chloro*-9-*xanthenylacetate Ethobromide*.—2-Diethylaminoethyl 3-chloro-9-xanthenylacetate hydrogen oxalate (10 g.) was shaken with excess of 10% aqueous sodium carbonate and benzene. The benzene extract was dried (K_2CO_3), a part of the benzene distilled off, and to the residual solution (100 c.c.) of the free ester ethyl bromide (20 c.c.) was added. The solution was gently refluxed for 5 days during which the quaternary *salt* (10 g.) precipitated as a microcrystalline hygroscopic powder (Found: *M*, 489; N, 3·0; Br, 16·6; Cl, 7·2%. $C_{23}H_{29}O_3NClBr$ requires *M*, 482·5; N, 2·9; Br, 16·6; Cl, 7·4%).

For preparing the methobromides it was preferable to keep an excess of methyl bromide and the tertiary ester in anhydrous ether at room temperature for 5 days. The methobromides separated in almost quantitative yield: The following were prepared in the same manner:

2-*Diethylaminoethyl* 9-*xanthenylideneacetate ethobromide*, needles, m. p. 168° (Found: *M*, 445. $C_{23}H_{26}O_3NBr$ requires *M*, 446).

2-*Diethylaminoethyl* 9-*xanthenylglycollate ethobromide* (Found: N, 3·8; Br, 17·6. $C_{23}H_{30}O_4NBr$ requires N, 3·0; Br, 17·2%).

2-*Diethylaminoethyl* 9-*xanthenylacetate ethobromide*, m. p. 164° (Found: C, 61·0; H, 6·7; N, 3·2; Br, 17·6. $C_{23}H_{30}O_3NBr$ requires C, 61·6; H, 6·7; N, 3·1; Br, 17·8%).

2-*Diethylaminoethyl xanthen*-9-*carboxylate ethobromide*, needles, m. p. 194° (Found: N, 3·5; Br, 19·0. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4).

N-2-*Diethylaminoethyl*-9-*xanthenylacetamide*.—9-Xanthenylacetic acid (12 g.) was refluxed with benzene (80 c.c.) and thionyl chloride (9 c.c.) for 2 hr., the solvent distilled off, benzene (60 c.c.) added, and this distilled off at reduced pressure. The residual acid chloride was dissolved in benzene (100 c.c.), 2-diethylaminoethylamine (13 g.) added during 10 min., and the mixture refluxed for 1 hr., cooled, and washed with N-sodium hydroxide and then water. The benzene solution was dried, concentrated, and diluted with ligroin (b. p. 60—80°). The *amide* (9 g.) separated in colourless needles, m. p. 122° (Found: C, 74·9; H, 7·9. $C_{21}H_{26}O_2N_2$ requires C, 74·6; H, 7·7%). The *ethobromide* was obtained by the benzene method in needles (Found: N, 6·4; Br, 18·2. $C_{23}H_{31}O_2N_2Br$ requires N, 6·3; Br, 17·9%).

In the same manner was prepared N-3-*diethylaminopropyl*-9-*xanthenylacetamide*, needles, m. p. 106° (Found: *M*, 348; C, 74·6; H, 8·0; N, 7·5%. $C_{22}H_{28}O_2N_2$ requires *M*, 352; C, 75·0; H, 8·0; N, 8·0%); the *ethobromide* had m. p. 130—140° (Found: *M*, 461. $C_{24}H_{33}ON_2Br$ requires *M*, 461).

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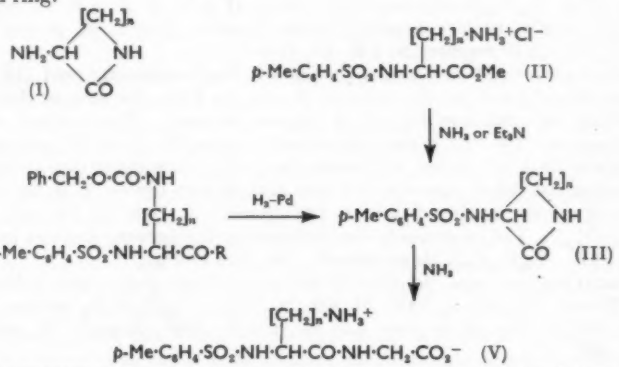
XUM

973. *The Formation of Cyclic Lactams from Derivatives of Basic Amino-acids.*

By B. C. Barrass and D. T. Elmore.

Cyclic 3-toluene-*p*-sulphonamidolactams (III; $n = 2$, 3, and 4) are formed by the action of ammonia or triethylamine on the methyl ester hydrochlorides of α-*N*-toluene-*p*-sulphonyldiamino-acids (II; $n = 2$, 3, and 4), and by hydrogenolysis of ω-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyldiamino-acid amides (IV; R = NH_2, $n = 2$, 3, and 4). The peptide linkages of α-*N*-toluene-*p*-sulphonylornithylglycine (V; $n = 3$) and γ-amino-α-toluene-*p*-sulphonamidobutyrylglycine (V; $n = 2$) are partly cleaved by methanolic or ethanolic ammonia at room temperature. α-*N*-Toluene-*p*-sulphonyl-lysylglycine (V; $n = 4$) is stable under these conditions, but is partly degraded in liquid ammonia at 100°. The infrared spectra of the lactams (III) are briefly discussed.

Ester hydrochlorides of lysine [1] and αγ-diaminobutyric acid [1,2] in presence of sodium alkoxides at room temperature readily afforded the cyclic 3-amino-lactams (I; $n = 4$ and 2 respectively). In addition, Rudinger [3] found that Curtius degradation of *N*-toluene-*p*-sulphonyl-L-glutamic acid γ-hydrazide gave 3-toluene-*p*-sulphonamidopyrrolid-2-one (III; $n = 2$). It has now been observed that methyl ester hydrochlorides of α-*N*-toluene-*p*-sulphonyldiamino-acids (II; $n = 2$, 3, and 4) in methanolic ammonia produce the cyclic 3-toluene-*p*-sulphonamido-lactams (III; $n = 2$, 3, and 4). The yields (88, 82, and 49% respectively) indicate that the seven-membered ring is less readily formed than the other two. A good yield of 3-toluene-*p*-sulphonamidopiperid-2-one (III; $n = 3$) also resulted from treatment of the ester hydrochloride (II; $n = 3$) with triethylamine in methanol at room temperature. The foregoing lactams were also afforded by the hydrogenolysis of ω-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyldiamino-amides (IV; R = NH_2, $n = 2$, 3, and 4) in methanol containing acetic acid. Both methods presumably involve nucleophilic attack by the uncharged ω-amino-group on the carbonyl-carbon atom. The second procedure gave theoretical yields of the pyrrolid-2-one (III; $n = 2$) and piperid-2-one (III; $n = 3$), whereas only 7% of the homopiperid-2-one (III; $n = 4$) was obtained, thereby emphasising even more markedly the relative difficulty of closing the seven-membered ring.



In view of the success of the foregoing reactions, the α-*N*-toluene-*p*-sulphonyl-peptides [4] (V; $n = 2$, 3, and 4) were kept in methanolic or ethanolic ammonia at room temperature

[1] Adamson, *J.*, 1943, 39.
[2] Wilkinson, *J.*, 1951, 104.
[3] Rudinger, *Coll. Czech. Chem. Comm.*, 1954, **19**, 365.
[4] Barrass and Elmore, *J.*, 1957, 3134.

for various lengths of time. Paper chromatography of the products revealed that the derivatives of αγ-diaminobutyric acid (V; $n = 2$) and ornithine (V; $n = 3$) were partly cleaved to glycine. In addition, the piperid-2-one (III; $n = 3$) was isolated from the products resulting from the degradation of the ornithine derivative (V; $n = 3$). α-*N*-Toluene-*p*-sulphonyl-lysylglycine (V; $n = 4$), however, was unchanged by this treatment and also by exposure to ethanolic ammonia at 60°. In liquid ammonia at 100°, on the other hand, some cleavage occurred, although chromatography revealed that an additional unknown ninhydrin-reacting substance was also formed. The greater stability of the lysine derivative than of the compounds of αγ-diaminobutyric acid and ornithine is consonant with the observations recorded above. It is interesting that Zaoral and Rudinger [5] have successfully reduced α-*N*-toluene-*p*-sulphonyl-L-ornithylglycine (V; $n = 3$) with sodium in liquid ammonia; presumably the desired reaction is much faster than the competing cyclisation and degradation at the b. p. of liquid ammonia.

In order to ascertain whether other basic peptides could be similarly degraded, tyrocidine was treated with ammonia under various conditions. In each case, the products were brought into reaction with 1-fluoro-2 : 4-dinitrobenzene,[6] then hydrolysed by acid, and the resulting 2 : 4-dinitrophenylamino-acids were identified by paper chromatography.[7] By this method, tyrocidine was found to be unaffected by ethanolic ammonia at room temperature or at 60°, or by liquid ammonia at 100°. This disappointing result would not seem to depend entirely on the electrophilic character of the carbonyl-carbon atom of the peptide linkage, since the $-I$ effect of the toluene-*p*-sulphonamido-group is apparently not much greater than that of an acylamino-group. Thus, the pK_a of *N*-acetylglycine [8] is 3·60, while that of *N*-toluene-*p*-sulphonylglycine [9] is 3·46. It is possible that the side-chain of the amino-acid linked to the carboxyl group of the basic amino-acid sterically hinders ring-closure. This is very likely in the case of tyrocidine [10] where the relevant amino-acid sequence is -orn.leu-.

The infrared spectra of the three cyclic lactams are of some interest. The νC=O band of 3-toluene-*p*-sulphonamido-L-pyrrolid-2-one is at 1698 cm.$^{-1}$, but for the two other compounds at 1658 cm.$^{-1}$, in general agreement with the spectra of unsubstituted cyclic lactams [11] and numerous cyclic ketones.[12] Further, there is no band which can be assigned to the amide-II vibration; this seems to be a characteristic property of cyclic lactams.[11,13] The weak band near 1600 cm.$^{-1}$ is attributed to skeletal vibrations of the aromatic ring. Finally, the two strong bands at 1168 and 1334—1339 cm.$^{-1}$ are doubtless due to the sulphonamide group, as reported earlier by several workers.[14]

Experimental

Optical rotations are quoted with 99% confidence limits. Infrared spectra were measured in pressed discs of potassium bromide with a Grubb-Parsons double-beam spectrometer and a rock-salt prism.

α-N-*Toluene*-p-*sulphonyl*-L-*lysine*.—This was obtained from ε-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine [4] by hydrogenolysis (90%) or by the action of hydrogen bromide

[5] Zaoral and Rudinger, *Proc. Chem. Soc.*, 1957, 176.
[6] Sanger, *Biochem. J.*, 1945, **39**, 507.
[7] Blackburn and Lowther, *ibid.*, 1951, **48**, 126.
[8] Zief and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2245.
[9] Lovén, *Z. phys. Chem.*, 1896, **19**, 456.
[10] Paladini and Craig, *J. Amer. Chem. Soc.*, 1954, **76**, 688; King and Craig, *ibid.*, 1955, **77**, 6627.
[11] Mecke and Mecke, *Chem. Ber.*, 1956, **89**, 343.
[12] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1954, pp. 127—128.
[13] Lenormant, *Bull. Soc. chim. France*, 1948, **15**, 33; Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949, p. 11; "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 390.
[14] Adams and Tjepkema, *J. Amer. Chem. Soc.*, 1948, **70**, 4204; Schreiber, *Analyt. Chem.*, 1949, **21**, 1168; Barnes, Gore, Liddel, and Williams, "Infra-red Spectroscopy," Reinhold Publ. Corp., New York, 1944, p. 87.

in acetic acid (46%). After recrystallisation from water, it had m. p. 263—264° (decomp.) [Kucherov and Ivanov [15] record m. p. 244° (decomp.)] (Found: C, 51·9; H, 6·7; N, 9·5. Calc. for $C_{13}H_{20}O_4N_2S$: C, 52·0; H, 6·7; N, 9·3%). The *hydrochloride* had m. p. 187—188° after recrystallisation from ethanol–ether (Found: C, 46·4; H, 6·2; N, 7·9; Cl, 10·4. $C_{13}H_{20}O_4N_2S$,HCl requires C, 46·4; H, 6·3; N, 8·3; Cl, 10·5%).

α-N-*Toluene*-p-*sulphonyl*-L-*ornithine* (97%), prepared as described for the racemate,[4] had m. p. 212—213° (decomp.) after recrystallisation from water (Found: C, 48·6; H, 6·7; N, 9·2; S, 10·9. $C_{12}H_{18}O_4N_4S,\frac{1}{2}H_2O$ requires C, 48·8; H, 6·5; N, 9·5; S, 10·9%).

γ-Amino-L-α-*toluene*-p-*sulphonamidobutyric Acid*.—Hydrogenolysis of γ-benzyloxycarboxyamido-L-α-toluene-*p*-sulphonamidobutyric acid [3, 4] in methanol containing a few drops of acetic acid afforded this *compound* (97%), m. p. 257—259° (decomp.) after recrystallisation from water (Found: C, 48·4; H, 5·8; N, 9·8. $C_{11}H_{16}O_4N_2S$ requires C, 48·5; H, 5·9; N, 10·3%).

α-N-*Toluene*-p-*sulphonyl*-L-*lysine methyl ester hydrochloride* (II; $n = 4$) was prepared (65%) from α-*N*-toluene-*p*-sulphonyl-L-lysine by the Fischer–Speier method. Recrystallised from ethanol–ether, it had m. p. 146—147° (Found: C, 47·7; H, 6·3; N, 8·3; S, 8·7; Cl, 9·6. $C_{14}H_{22}O_4N_2S$,HCl requires C, 47·9; H, 6·6; N, 8·0; S, 9·1; Cl, 10·1%).

α-N-*Toluene*-p-*sulphonyl*-L-*ornithine methyl ester hydrochloride* (II; $n = 3$), prepared by the same method (84% yield), had m. p. 152—153° after recrystallisation from ethanol–ether (Found: C, 45·9; H, 6·7; N, 8·2; S, 9·2. $C_{13}H_{20}O_4N_2S$,HCl requires C, 46·4; H, 6·2; N, 8·3; S, 9·5%). The DL-*compound* had m. p. 184·5—185·5° (Found: C, 46·5; H, 6·2; N, 8·4; S, 9·4%).

Methyl γ-Amino-L-α-*toluene*-p-*sulphonamidobutyrate Hydrochloride* (II; $n = 2$).—Obtained in almost theoretical yield by the same method, this *compound* had m. p. 199·5—200·5° after recrystallisation from methanol–ether (Found: C, 44·3; H, 6·1; N, 8·8; S, 9·4. $C_{12}H_{18}O_4N_2S$,HCl requires C, 44·6; H, 5·9; N, 8·7; S, 9·9%).

ε-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*lysine Methyl Ester* (IV; R = OMe, $n = 4$).—ε-*N*-Benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine (1 g.) was dissolved in methanol (10 c.c.) and benzene (10 c.c.) containing toluene-*p*-sulphonic acid (0·1 g.). The solution was slowly distilled during 6 hr., more methanol–benzene being added as required. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed successively with 10% aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure. The *ester* (0·92 g., 90%), crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 80—81° (Found: C, 59·0; H, 6·3; N, 5·6. $C_{22}H_{28}O_6N_2S$ requires C, 58·9; H, 6·2; N, 6·2%).

δ-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*ornithine methyl ester* (IV; R = OMe, $n = 3$) was prepared by the same method (90%). It crystallised from ether–light petroleum (b. p. 40—60°), and had m. p. 97—98° (Found: C, 57·7; H, 5·9; N, 6·4. $C_{21}H_{26}O_6N_2S$ requires C, 58·0; H, 6·0; N, 6·4%). The DL-*compound* had m. p. 93·5—94·5° [from benzene–light petroleum (b. p. 40—60°)] (Found: C, 58·3; H, 6·3; N, 6·1%).

Methyl γ-Benzyloxycarboxyamido-L-α-*toluene*-p-*sulphonamidobutyrate* (IV; R = OMe, $n = 2$).—Prepared by the same method (91%), this *ester* crystallised from benzene–ether–light petroleum (b. p. 40—60°) and had m. p. 103·5—104·0° (Found: C, 57·0; H, 5·9; N, 7·0. $C_{20}H_{24}O_6N_2S$ requires C, 57·1; H, 5·8; N, 6·7%).

ε-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*lysine amide* (IV; R = NH_2, $n = 4$) was afforded (79%) by treatment of the methyl ester (IV; R = OMe, $n = 4$) with ethanolic ammonia at room temperature for 2 days. Crystallised from ethanol or dioxan–light petroleum (b. p. 60—80°), it had m. p. 157—158° (Found: C, 57·8; H, 6·3; N, 10·3; S, 6·9. $C_{21}H_{27}O_5N_3S$ requires C, 58·2; H, 6·2; N, 9·7; S, 7·4%).

δ-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*ornithine amide* (IV; R = NH_2, $n = 3$), obtained in theoretical yield and crystallised from propan-1-ol, had m. p. 135—136° (Found: C, 56·8; H, 6·0; N, 10·1. $C_{20}H_{25}O_5N_3S$ requires C, 57·3; H, 6·0; N, 10·0%). The DL-*compound* had m. p. 143—144° [from acetone–light petroleum (b. p. 60—80°)] (Found: C, 56·9; H, 5·9; N, 10·4%).

γ-Benzyloxycarboxyamido-α-*toluene*-p-*sulphonamido*-L-*butyramide* (IV; R = NH_2, $n = 2$).—Prepared in the same manner, this *compound* (92%) had m. p. 165—166° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 55·8; H, 5·6; N, 10·6. $C_{19}H_{23}O_5N_3S$ requires C, 56·3; H, 5·7; N, 10·4%).

[15] Kucherov and Ivanov, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 1243.

3-Toluene-p-sulphonamido-L-homopiperid-2-one (III; $n = 4$).—(*a*) α-*N*-Toluene-*p*-sulphonyl-L-lysine methyl ester hydrochloride (2·5 g.) in methanol (5 c.c.) and chloroform (20 c.c.) was treated with a saturated solution of ammonia in chloroform (250 c.c.). The resulting suspension was shaken for 5 min., then filtered, and the filtrate was evaporated to small bulk under reduced pressure. The residue was left in saturated methanolic ammonia (100 c.c.) at room temperature for 2 days. After concentration under reduced pressure, the *product* recrystallised from methanol, then having m. p. 210—212°, $[\alpha]_D^{23}$ +111·5° ± 0·5° (*c* 1·15 in dimethylformamide) (Found: C, 54·9; H, 6·4; N, 10·2; S, 11·5. $C_{13}H_{18}O_3N_2S$ requires C, 55·3; H, 6·4; N, 9·9; S, 11·4%). The infrared spectrum had bands at 3370 m, 3210 m, 3030 w, 2905 m, 2845 m, 1658 s, 1599 m, 1496 m, 1443 s, 1414 m, 1376 m, 1336 s, 1294 m, 1279 m, 1251 w, 1225 w, 1168 s, 1116 w, 1086 s, 1068 s, 1034 w, 1025 w, 982 w, 953 w, 927 s, 888 m, 850 w, 829 m, 821 s, 805 m, 775 m cm.$^{-1}$.

(*b*) ε-*N*-Benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine amide (2·87 g.) was hydrogenolysed over palladous oxide (0·3 g.) in methanol (50 c.c.) and acetic acid (1 c.c.). After filtration and evaporation under reduced pressure, the residual lactam (0·13 g., 7%) was recrystallised first from ethanol–ether and then methanol; it had m. p. 210—212°, undepressed by admixture with the above sample. The infrared spectra were identical.

3-Toluene-p-sulphonamido-L-piperid-2-one (III; $n = 3$).—(*a*) and (*b*). This *lactam* was prepared from both α-*N*-toluene-*p*-sulphonyl-L-ornithine methyl ester hydrochloride (82%) and δ-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-ornithine amide (~100%) by the methods given for the homopiperid-2-one analogue. Recrystallised from methanol, it had m. p. 184—185°, $[\alpha]_D^{24}$ +60·5° ± 0·3° (*c* 1·8 in dimethylformamide) (Found: C, 53·4; H, 5·8; N, 10·4; S, 11·9. $C_{12}H_{16}O_3N_2S$ requires C, 53·7; H, 6·0; N, 10·4; S, 11·9%). The infrared spectra of the two samples were identical and had bands at 3190 m, 3100 m, 2905 m, 2850 m, 1658 s, 1599 w, 1505 w, 1459 m, 1432 m, 1334 s, 1320 m, 1289 w, 1268 w, 1214 w, 1168 s, 1135 m, 1099 s, 1025 w, 989 w, 951 m, 937 sh, 902 w, 871 w, 855 w, 818 m, 812 m, 798 m, 709 w cm.$^{-1}$.

(*c*) α-*N*-Toluene-*p*-sulphonyl-L-ornithine methyl ester hydrochloride (0·337 g.) and triethylamine (0·101 g.) in methanol (5 c.c.) gave the same lactam (0·200 g., 75%) during 4 days at room temperature. Recrystallised from methanol, it had m. p. and mixed m. p. 184—185°.

The DL-*compound* (80%) was prepared by method (*a*). Recrystallised from methanol–light petroleum (b. p. 40—60°), it had m. p. 183·5—184·0° (Found: C, 53·4; H, 6·1; N, 10·0%).

3-Toluene-*p*-sulphonamido-L-pyrrolid-2-one (III; $n = 2$) was prepared by methods (*a*) (88% yield) and (*b*) (~100% yield). Recrystallised from methanol, it had m. p. 206—207° (in agreement with Rudinger [3]), $[\alpha]_D^{23}$ +14·6° ± 0·3° (*c* 1·27 in dimethylformamide) (Found: C, 51·6; H, 5·5; N, 10·6; S, 12·3. Calc. for $C_{11}H_{14}O_3N_2S$: C, 51·9; H, 5·6; N, 11·0; S, 12·6%). The infrared spectra of the two samples were identical and had bands at 3230 m, 3100 m, 2890 m, 1698 s, 1610 w, 1482 sh, 1462 m, 1448 m, 1383 w, 1339 s, 1322 sh, 1308 m, 1290 m, 1255 w, 1209 w, 1196 w, 1168 s, 1148 s, 1100 m, 1065 w, 1025 w, 1006 w, 947 w, 916 m, 896 m, 858 w, 842 w, 818 m, 801 w cm.$^{-1}$.

Action of Ammonia on α-N-*Toluene-p-sulphonylpeptides.*—(*a*) α-*N*-Toluene-*p*-sulphonyl-DL-ornithylglycine [4] (V; $n = 3$) (170 mg.) in saturated methanolic ammonia (50 c.c.) was kept in a sealed tube at room temperature for a week. After evaporation under reduced pressure, paper chromatography of a sample in butan-1-ol–acetic acid–water (4 : 1 : 5) revealed glycine as well as some starting material. The residue was extracted with dilute hydrochloric acid and filtered. The insoluble fraction (45 mg.) was dried *in vacuo* over phosphoric oxide. Recrystallised from aqueous methanol and then from methanol–light petroleum (b. p. 40—60°), it had m. p. 182—183° alone and in admixture with 3-toluene-*p*-sulphonamido-DL-piperid-2-one described above. The infrared spectra were identical, but slightly different from that of the L-stereoisomer.

(*b*) γ-Amino-α-toluene-*p*-sulphonamido-L-butyrylglycine [4] (V; $n = 2$) in saturated methanolic ammonia (10 c.c.) was left in a stoppered tube at room temperature for 1 day. Paper chromatography revealed that some degradation to glycine had occurred.

(*c*) α-*N*-Toluene-*p*-sulphonyl-L-lysylglycine [4] (V; $n = 4$) (100 mg.) in liquid ammonia (4 c.c.) was heated at 100° for 20 hr. in an open tube enclosed in a small stainless steel bomb. After ammonia had been allowed to evaporate, the residue was dissolved in aqueous ethanol and examined by paper chromatography. Two ninhydrin-positive spots were identified as glycine (R_F 0·11) and α-*N*-toluene-*p*-sulphonyl-L-lysylglycine (R_F 0·36); a further spot (R_F 0·47) was not identified, but was distinguished from α-*N*-toluene-*p*-sulphonyl-L-lysine (R_F 0·51). No

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degradation of α-*N*-toluene-*p*-sulphonyl-L-lysylglycine occurred in saturated methanolic ammonia at room temperature or at 60° during 24 hr.

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974. *The Amides of 4-Hydroxy- and 4-Alkoxy-*isophthalic *Acids.*

By J. M. Z. GLADYCH, A. S. LINDSEY, and E. P. TAYLOR.

Some mono- and di-amides of 4-hydroxy- and 4-alkoxy-*iso*phthalic acids are prepared.

THE reported analgesic and antipyretic properties of 4-hydroxy*iso*phthalic acid [1] suggest that the mono- and di-amides of this and the related 4-alkoxy-acids might be of interest. Some of our preliminary work has already been reported.[2]

Jacobsen [3] claimed to prepare 4-hydroxy*iso*phthalamide by treating the dimethyl or diethyl ester with alcoholic ammonia. We found the major product to be the alkyl 3-carbamoyl-4-hydroxybenzoate, only a small amount of the diamide being isolated. However, treatment of the dimethyl ester with liquid ammonia for 30 hr. at 100—110° gave the diamide in good yield, although 15 hours' heating gave the ester-amide.

4-Alkoxy*iso*phthalic acids, on treatment with thionyl chloride followed by ammonium hydroxide or carbonate, were smoothly converted into the diamides; in one experiment with 4-methoxy*iso*phthalic acid in which ammonium carbonate was added before complete removal of thionyl chloride, the product contained considerable quantities of a methoxy-cyanobenzamide which must have arisen by dehydration. By the general method 4-hydroxy*iso*phthalic acid gave apparently a mixture of the isomeric 1- and 3-monoamide (independent preparation of the latter will be described elsewhere). We have confirmed the orientation of the latter by isolating it, although in small yield, from a Kolbe–Schmitt carboxylation of the potassium derivative of salicylamide.

EXPERIMENTAL

4-Hydroxyisophthalamide.—Dimethyl 4-hydroxy*iso*phthalate (21 g.) and liquid ammonia (approx. 50 ml.) were heated in a rotating bomb at 100—110° for 30 hr. After cooling, the residue was dissolved in water and filtered from a trace of insoluble matter, and the filtrate acidified with 2N-hydrochloric acid. The precipitate was filtered off, washed with water, made into a slurry with an excess of 5% aqueous sodium hydrogen carbonate, filtered, washed with water, and dried. The crude solid [16 g.; m. p. 258—259 (decomp.)] was recrystallised once from ethanol and twice from aqueous dimethylformamide, to give 4-hydroxy*iso*phthalamide (10 g.), prisms, m. p. 264—264·5° (decomp.) (Found: C, 53·6; H, 4·7; N, 15·2. Calc. for $C_8H_8O_3N_2$: C, 53·3; H, 4·5; N, 15·6%). Jacobsen [3] records m. p. 250°.

When this experiment was repeated but with the addition of ethanol (50 ml.) the crude product (17·7 g.), obtained by evaporation of the mixture, had m. p. 216—228° (decomp.). Repeated fractional crystallisation from ethanol and aqueous dimethylformamide gave the diamide (1 g.) [m. p. and mixed m. p. 264—264·5° (decomp.)] and methyl 3-carbamoyl-4-hydroxybenzoate (4·2 g.), m. p. 256—257°.

Methyl 3-Carbamoyl-4-hydroxybenzoate.—Dimethyl 4-hydroxy*iso*phthalate (21 g.) and liquid ammonia (approx. 40 ml.) were heated in a rotating bomb at 90—100° for 15 hr., then dissolved in water and acidified as before, yielding 16·5 g. of material, m. p. 249—250° (decomp.). After

[1] Chesher, Collier, Robinson, Taylor, Hunt, Jones, and Lindsey, *Nature*, 1955, **175**, 206; Collier and Chesher, *Brit. J. Pharmacol.*, 1956, **11**, 20.
[2] Hunt, Jones, and Lindsey, *Chem. and Ind.*, 1955, 417; Gladych and Taylor, *J.*, 1956, 4678.
[3] Jacobsen, *Ber.*, 1878, **11**, 380.

three recrystallisations from ethanol, the *ester-amide* was obtained as rosettes, m. p. 256—257° (Found: C, 55·4; H, 4·6; N, 6·8. $C_9H_9O_4N$ requires C, 55·4; H, 4·65; N, 7·2%).

The solid (2·0 g.) was kept in N-sodium hydroxide (30 ml.) at 20° for 5 hr., then acidified with 2N-hydrochloric acid. The precipitate was washed with water and dried *in vacuo*. The crude product had m. p. 296—297° (decomp.) alone or mixed with the 3-monoamide of 4-hydroxy*iso*phthalic acid. This and the following experiment confirmed the structure of the ester-amide.

The 3-monoamide (3·6 g.), methanol (50 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (1·0 g.) were heated together for 15 hr. under a Dean and Stark apparatus. After cooling, the solid was filtered off, washed with a little benzene, and dried. The crude ester-amide (2·6 g., m. p. 254—255°) crystallised from absolute ethanol in rosettes, m. p. 256—257°.

Methyl 3-carbamoyl-4-hydroxybenzoate (0·5 g.) was also obtained when dimethyl 4-hydroxy*iso*phthalate (2·0 g.) was heated for 2 hr. in boiling aqueous ammonia (25 g., *d* 0·88).

Ethyl 3-Carbamoyl-4-hydroxybenzoate.—Diethyl 4-hydroxy*iso*phthalate (4·0 g.), ethanol (60 ml.), and liquid ammonia (approx. 30 ml.) were heated in a rotating bomb at 100° for 9 hr. After evaporation the residual *ester-amide* (3·5 g.; m. p. 216—218°) recrystallised from ethanol (after charcoal) as needles, m. p. 225—226° (Found: C, 57·3; H, 5·1; N, 6·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). Hydrolysis gave the 3-monoamide, m. p. and mixed m. p. 295—296° (decomp.), in excellent yield.

Treatment of 4-Hydroxyisophthalic Acid with Thionyl Chloride and Ammonia.—4-Hydroxy-*iso*phthalic acid (10 g.) and thionyl chloride (35 ml.) were heated under reflux for 6 hr. The excess of thionyl chloride was then distilled off as azeotrope with benzene, the solvent completely removed, and the oil poured into stirred aqueous ammonia (*d* 0·88) at 0°. The mixture was diluted with water, acidified with 2N-hydrochloric acid, and filtered, and the precipitate washed with water and dried. The resulting yellow solid [5·3 g.; m. p. 249—250° (decomp.)] was dissolved in 2N-sodium hydroxide, reprecipitated with 2N-hydrochloric acid, filtered off, washed with water, and dried. The faintly yellow product had m. p. 247—249° (decomp.) which was raised on admixture with the 1-monoamide [mixed m. p. 253—254° (decomp.)] or the 3-monoamide of 4-hydroxy*iso*phthalic acid [mixed m. p. 251—252° (decomp.)]. Recrystallisation from aqueous dimethylformamide gave needles, m. p. 259—260° (decomp.) [mixed m. p. with the 1-amide, 258—259° (decomp.); with the 3-amide, 263—264° (decomp.)] (Found: C, 53·2; H, 3·8; N, 7·8. Calc. for $C_9H_7O_4N$: C, 53·0; H, 3·9; N, 7·7%). The product therefore seems to be a mixture of monoamides. [A 1 : 1 mixture of the monoamides has m. p. 266—267° (decomp.), and a 2 : 1 mixture of 1- and 3-amide has a m. p. of 257—257·5° (decomp.).]

4-Alkoxyisophthalic Acids.—Dimethyl 4-hydroxy*iso*phthalate (1 mol.), alkyl bromide (or iodide) (2 mols.), and anhydrous potassium carbonate (1 mol.) in ethanol were refluxed for 35—40 hr., then cooled and filtered. The filtrate was concentrated to small bulk, diluted with water, and extracted with benzene. The benzene extract was washed with 2N-sodium hydroxide and water, shaken with magnesium sulphate, filtered, and evaporated. The crude ester was then hydrolysed for 15 hr. at room temperature with 2N-sodium hydroxide (4 mols.), enough alcohol being added to effect dissolution. The solution was then acidified with 2N-hydrochloric acid and cooled. The crude alkoxy-acid was filtered off, washed with water, dried, and recrystallised.

The following 4-alkoxy*iso*phthalic *acids* are new: *Benzyloxy*, prisms [from acetone–light petroleum (b. p. 40—60°)], m. p. 194—195° (crude yield 71%) (Found: C, 66·5; H, 4·7. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·45%); *allyloxy*, needles (from aqueous methanol) (62%), m. p. 222—223° (decomp.) (Found: C, 59·4; H, 4·4. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%); *iso-butoxy*, needles (from aqueous ethanol) (5%), m. p. 211—212° (Found: C, 60·3; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%); sec.-*butoxy*, needles (from aqueous ethanol) (5%), m. p. 177—178° (Found: C, 61·0; H, 5·9%).

We also prepared the following known 4-alkoxy*iso*phthalic acids:

Methoxy, m. p. 276° (decomp.) (as recorded [4]), ethoxy, m. p. 261—262° (lit.,[5] 259—260°), *n*-propoxy, m. p. 231—232° (lit.,[5] 214—215°) (Found: C, 58·9; H, 5·9. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%), *iso*propoxy, m. p. 224—225° (lit.,[5] 230—231°) (Found: C, 59·3; H, 5·4%), and *n*-butoxy, m. p. 195—196° (lit.,[5] 193—195°).

[4] Hunt, Jones, and Lindsey, *J.*, 1956, 3099.

[5] Mndzhoyan and Aroyan, *Izvest. Akad. Nauk. Armyan. S.S.R., Ser. Fiz.-Mat., Estestven i Tekh Nauk*, 1955, **8**, (6), 29 (*Chem. Abs.*, 1956, **50**, 11,982).

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On treatment of the 4-alkoxy*iso*phthalic acids with thionyl chloride and aqueous ammonia (or in some cases powdered ammonium carbonate), as described above for 4-hydroxy*iso*phthalic acid, the corresponding diamides were obtained in good yield, namely: *methoxy*, needles (from ethanol), m. p. 246—247° (crude yield 30%) (Found: C, 55·7; H, 5·4; N, 14·4. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%), *ethoxy*, needles (from aqueous alcohol) (79%), m. p. 275—276° (decomp.) (Found: C, 58·2; H, 5·7; N, 13·3. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%), n-*propoxy*, needles (from aqueous dimethylformamide) (78%), m. p. 243—244° (decomp.) (Found: C, 59·7; H, 6·1; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%), iso*propoxy*, needles (from ethanol) (62%), m. p. 197—198° (Found: C, 59·4; H, 6·6; N, 12·7. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·4; N, 12·6%), *allyloxy*, cream-coloured needles (from aqueous dimethylformamide) (100%), m. p. 220—221° (decomp.) (Found: C, 59·5; H, 5·5; N, 12·7. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%), n-*butoxy*, needles (from aqueous dimethylformamide) (90%), m. p. 261—262° (Found: C, 61·5; H, 7·0; N, 11·8. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%), and *benzyloxy*, needles (from ethanol) (100%), m. p. 227—228° (Found: C, 66·7; H, 5·4; N, 10·5. $C_{16}H_{14}O_3N_2$ requires C, 66·7; H, 5·2; N, 10·4%).

With 4-methoxy*iso*phthalic acid, when ammonium carbonate was added before complete removal of the thionyl chloride, the product contained appreciable quantities of a *methoxycyanobenzamide*, which crystallised from ethanol as needles, m. p. 256—257° (Found: C, 61·5; H, 4·7; N, 15·9. $C_9H_8O_3N_2$ requires C, 61·4; H, 4·6; N, 15·9%. The infrared spectrum revealed a band of medium strength at 2232 cm.$^{-1}$ (C≡N). Hydrolysis with hot 50% (v/v) sulphuric acid gave 4-methoxy*iso*phthalic acid (mixed m. p.).

4-*n*-Butoxy*iso*phthalamide was also prepared in good yield by heating 4-hydroxy*iso*phthalamide (1·8 g.) with *n*-butyl bromide (3·0 g.), anhydrous potassium carbonate (1·4 g.), and ethanol (50 ml.) under reflux for 40 hr.

Structure of the 3-Monoamide of 4-Hydroxyisophthalic Acid.—The potassium derivative of salicylamide (3·6 g.) and solid carbon dioxide (20 g.) were heated in a bomb at 165—172° for 3 hr. at a maximum pressure of 22 atm. After cooling, the residue was extracted with cold water, leaving 0·7 g. of insoluble salicylamide (m. p. and mixed m. p. 140—141°). The aqueous extract was acidified with 2N-hydrochloric acid. The precipitate was filtered off, washed with water, dried [0·5 g., m. p. 240—241° (decomp.)], and recrystallised twice from aqueous dimethylformamide, giving light brown needles, m. p. 244·5—245° (decomp.) [Wohl [6] gives m. p. 245° (decomp.) for the 3-amide of 2-hydroxy*iso*phthalic acid]. The acid filtrate obtained as above deposited a second crop (0·04 g.) of crystals. After two recrystallisations from aqueous dimethylformamide these had m. p. 294—295° (decomp.), mixed m. p. with the 3-monoamide of 4-hydroxy*iso*phthalic acid (prepared by ammonolysis of the 3-methyl ester) 297° (decomp.).

Some of the microanalyses were carried out by Miss M. Corner and the staff of the microanalytical section of the Chemical Research Laboratory, Teddington. One of us (A. S. L.) thanks Dr. Idris Jones for his interest; the others thank Mr. I. J. Gibson for technical assistance. We are indebted to the Directors of Allen and Hanburys Ltd. and the Director of the Chemical Research Laboratory, Teddington, for permission to publish this work.

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[6] Wohl, *Ber.*, 1910, **43**, 3483.

975. *Dependence of Physical Properties on Atomic Size and Atomic Number. Part V.* Boiling Points of Halides.*

By G. R. Somayajulu and Santi R. Palit.

In a sequence of halides the b. p. is a linear function of the surface area of the halogen atoms in the molecule. The b. p.s of two similar sequences are also linearly related. A generalised scheme giving linear correlation between b. p.s of any sequence of halides and those of the halogens is presented.

Somayajulu [1] has empirically shown that in any sequence of compounds of the general formula RX_n, where X is a halogen and R any atom or atomic group, the boiling point is linearly related to the sum of the effective atomic numbers (Z') of the halogen atoms in RX_n, the value of Z' being empirically taken as 9, 17, 22, and 30 for F, Cl, Br, and I respectively, in place of their true atomic numbers (Z) of 9, 17, 35, and 53 respectively. Thus

$$T_b = a\sum Z' + b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

a and b being constants for any particular sequence.

The above relation is highly successful and consistent in describing the boiling-point

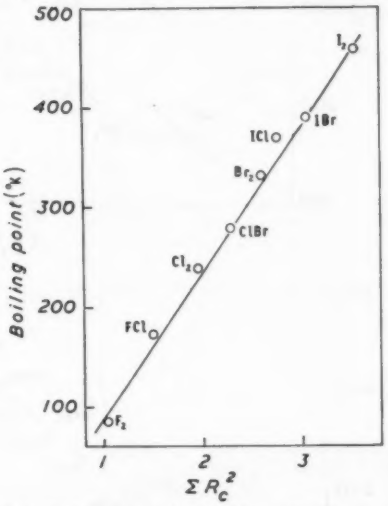


Fig. 1. *Boiling point as a function of the surface area for the halogens and diatomic interhalogens.*

trend in many series of compounds, such as interhalogens, tetrahalides of silicon and carbon, and many other halides. The objection due to the arbitrary nature of Z' can be overcome by using the square of the atomic radius (*i.e.*, a fraction of surface area) in place of Z', this giving [2] similar correlation with T_b. The present paper demonstrates the validity of such simple inter-relations and their consequence, and the general validity of all such relations for a wide variety of sequences.

Boiling Point and Atomic Size.—In the halogen series,[2] Z' is proportional to R_c^2 where R_c is the covalent atomic radius of the halogen atom. Substituting this value of Z' in equation (1), we immediately obtain

$$T_b = a_1\sum R_c^2 + b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where a_1 and b are constants, *i.e.*, in a sequence of similar compounds containing halogens, the boiling point is linearly related to the sum of the squares of the covalent radii of the

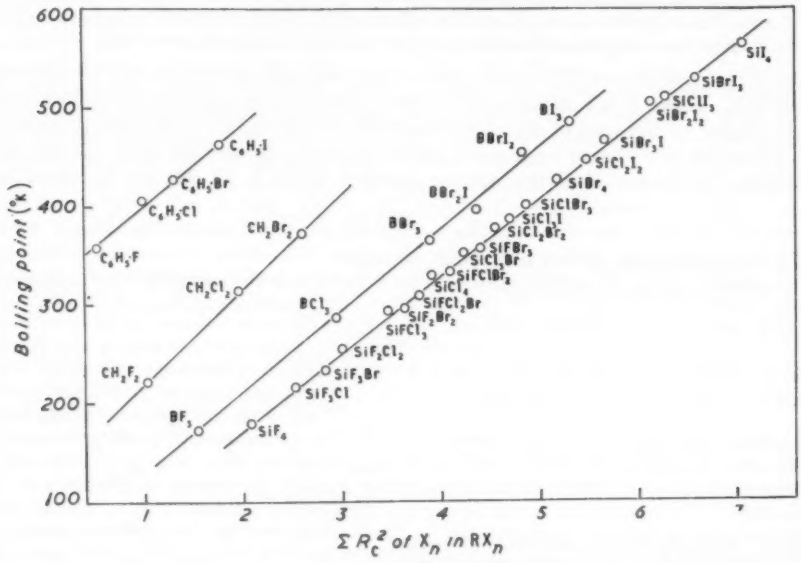
* Parts I—IV are considered to be, respectively, refs. 1 and 2, *J. Chem. Phys.*, 1957, **26**, 807, and *J.*, 1957, 2540.

[1] Somayajulu, *Indian J. Phys.*, 1956, **30**, 258.

[2] Somayajulu and Palit, *ibid.*, p. 262.

halogen atoms in the molecule (Figs. 1 and 2). The values of R_c used for the halogens are by Schomaker and Stevenson,[3] namely 0·72, 0·99, 1·14, and 1·33 Å respectively, for F, Cl, Br, and I.

FIG. 2. *Boiling point as a function of the surface area for phenyl halides, methylene halides, boron trihalides, and silicon tetrahalides.*



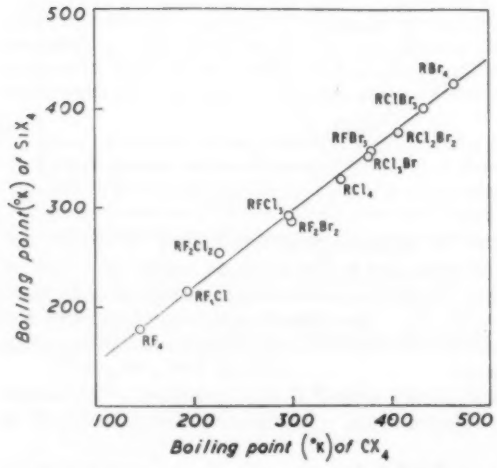


FIG. 3. *Boiling point of silicon tetrahalides as a function of boiling point of carbon tetrahalides.*

Fig. 1 demonstrates the validity of relation (2) for the halogens and interhalogens, X_2. In all cases where Somayajulu's relation is valid,[1] eqn. (2) would also be applicable and graphs of the type of Fig. 1 would be obtained. We give in Fig. 2 a few representative graphs for four typical sequences of the type RX, RX_2, RX_3, and RX_4, represented by phenyl halides, methylene halides, boron trihalides, and silicon tetrahalides.

[3] Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 37.

Correlation between T_b of Two Sequences.—If eqn. (1) [or (2)] is valid, T_b of two sequences of the same type would be linearly related, *i.e.*,

$$T_b' = \alpha T_b'' + \beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where α and β are constants. Thus, we find the simple result that T_b of halides of, say, carbon would be linearly related to that of any other sequence of halides, say, of silicon, provided they contain the same number of halogen atoms in the molecule and corresponding members of the two sequences are compared. The validity of this is shown by

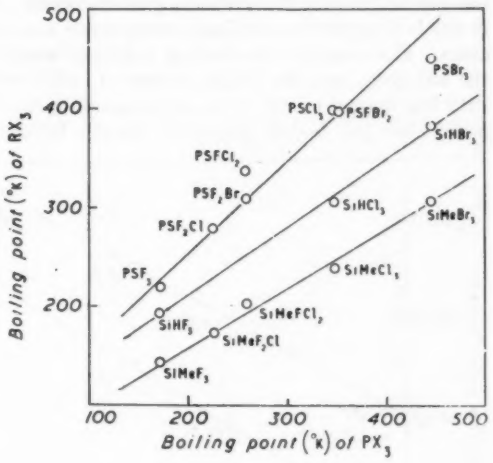


FIG. 4. *Boiling point of the sequences* PSX_3, $SiHX_3$, *and* $SiMeX_3$ ($T_b - 100$) versus *boiling point of* PX_3.

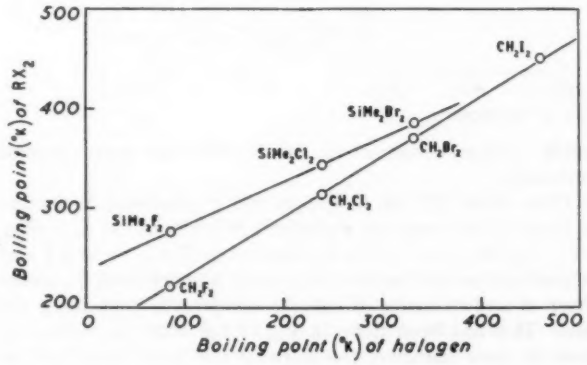


FIG. 5. *Boiling point of* CH_2X_2 *and* $SiMe_2X_2$ versus *boiling point of* X_2.

Fig. 3. We can thus predict the boiling point of an unknown silicon halide from that of the corresponding carbon halide and *vice versa*.

For three trihalide series, phosphorus trihalides being taken as the basis for comparison, Fig. 4 shows that eqn. (3) is fairly held, and that even in such complicated compounds as phosphorus thiohalides it is valid.

In Fig. 5, T_b of the simplest carbon dihalides, plotted against that of the halogens (no b. p. data for mixed dihalides are available), again shows the relation to be valid, and we conclude that the boiling-point trend of the halogens is somehow maintained in combination. Similar remarks apply to the boiling points of dimethylsilicon dihalides.

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Fig. 6 shows that eqn. (3) fairly well represents the behaviour of some monohalogen derivatives. From the method of derivation of eqn. (3) we can use T_b for pure halogens as our basis for comparison, for monohalides as for dihalides, so here also we conclude that the boiling-point trend of the pure halogens somehow persists in their monohalogen derivatives.

A remarkable feature of Figs. 3—6 is that, though the intercepts vary widely, the variation of the slope, α, is small and its value is not far from unity, which shows that a and a_1 are of the same order of magnitude for all sequences. The much lower (almost half) slope in Fig. 6 is only an apparent exception to this, because here we compare a monohalogen series with the diatomic pure halogens. It is surprising that these general trends in the boiling points of halogen compounds has not been earlier observed except for a few cases. For example, the boiling points of halides are [4,5] linear with the polarisability of the halogens, and the boiling points of halide sequence of rare-gas structure are [6] linear with the boiling points of the corresponding rare gases. Very recently Macdiarmid [7] has noted that the boiling points of dimethylsilicon dihalides are linear with those of the

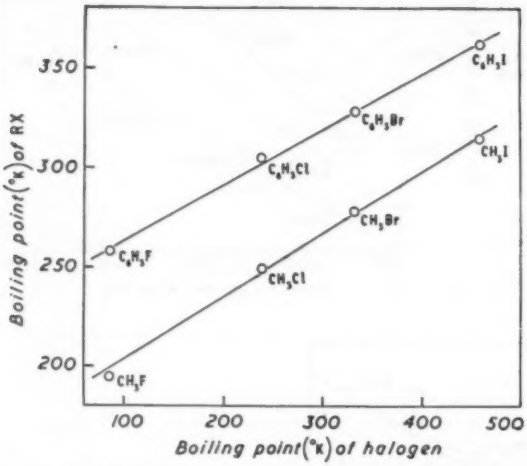


FIG. 6. *Boiling point of* CH_3X *and* C_6H_5X versus *boiling point of* X_2.

corresponding carbon compounds. These observations fit in with our more general relations discussed here and previously.

A Generalised T_b versus T_b *Plot.*—Eqn. (3) can be graphically represented in a more general way. From the linear form of the foregoing equations, a fictitious set of boiling points (°K), *viz.*, half the T_b of F_2, Cl_2, Br_2, and I_2, can be allotted to F, Cl, Br, and I and such boiling points properly summed can be used as the abscissa in a generalised T_b *versus* T_b plot for comparison with those of any sequence of halogen compounds containing the same number of halogen atoms. This has been done in Fig. 7 for many sequences of halogen compounds. All sequences show linearity, the slope of the lines being not far from unity for all of them. The intercept depends among other factors on the mass and structure of the molecules. Such diagrams are useful in predicting the order of boiling points of a given sequence of halogenated compounds, and, knowing the values of any two, those of the others. This is worth while, as there are 4, 10, 20, and 35 compounds in any sequence of RX, RX_2, RX_3, and RX_4 type respectively.

Boiling Point and Z'.—Though eqns. (2) and (3), being free from the objection of

[4] Huckel, "Structural Chemistry of Inorganic Compounds," Vol. II, Elsevier, New York, 1951.
[5] Van Arkel, "Molecules and Crystals," 2nd Edn., Butterworths Scientific Publications, London, 1947.
[6] Carlson, *Ber.*, 1925, **58**, 1747.
[7] Macdiarmid, *Quart. Rev.*, 1956, **10**, 208.

arbitrariness of Z' value, appear to be of more fundamental significance than eqn. (1), we do not consider them any better for the following reasons. First, not only are the same values of S, where $Z' = Z - S$, consistently used for halogens, but the same values cause good correlations in sequences of elements of other groups of the Periodic Table. Secondly, not only T_b but also many other properties of various sequences are correlated simply [1] with Z'. Thirdly, the most important argument for using Z' values is that the sequence relations discussed here are all linear, so it is immaterial whether the summation in $\sum Z'$ or $\sum R_e^2$ concerns only the halogen atoms in the molecule or the whole molecule, and our choice of the former is a mere convenience. In a homologous series, however, T_b is often related linearly [8] to $\sqrt{\sum Z}$ or $\sqrt{\sum Z'}$ of the whole molecule, and in such cases relations of the

FIG. 7. *Boiling point of* SiH_3X, $SiMe_2X_2$, BX_3, *and* CX_4 versus *boiling point of* X, X_2, X_3, *and* X_4 *respectively.*

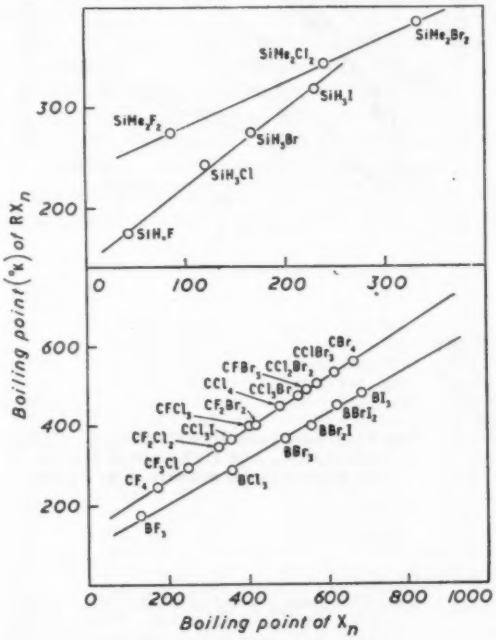
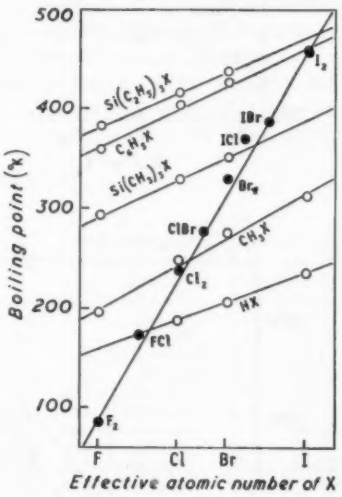


FIG. 8. *Boiling point of* X_2, HX, CH_3X, $SiMe_3X$, C_6H_5X, *and* $Si(C_2H_5)_3X$ versus *effective atomic number of* X.



type of eqn. (2) or (3) are either inapplicable or difficult to apply. We have therefore explored below the validity of eqn. (1), but clearly wherever eqn. (1) is found to be applicable, eqns. (2) and (3) and also the generalised plot are necessarily valid.

Boiling Points of Halides of the Type RX.—We have plotted in Fig. 8 the boiling points of halides of this type against Z'. In each case a straight line is obtained in conformity with the relation given by Somayajulu.[1] Among the hydrogen halides, hydrogen fluoride, which is associated, is an exception by boiling at a higher temperature than expected. From the observed T_b for hydrogen fluoride, and assuming eqn. (1) to be valid for HX, we have calculated the apparent $\sum Z$ for HF and thence its average degree of association, which comes out at 4·5. Unfortunately, no method is available for independent verification of this value.

We have also plotted in Fig. 8 the boiling points of the halogens and the interhalogens of AB type, and all of them fall fairly well on a straight line. Our equations are only

[8] Somayajulu and Palit, *J.*, 1957, 2540.

FIG. 9.

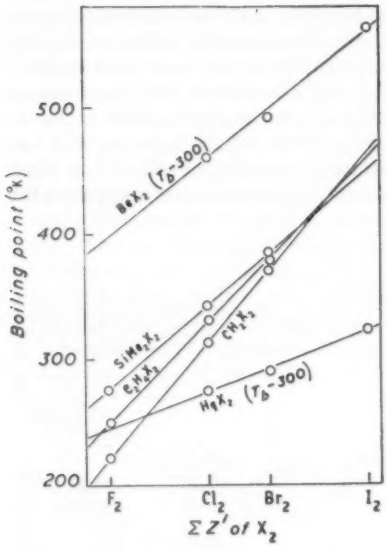


FIG. 10.

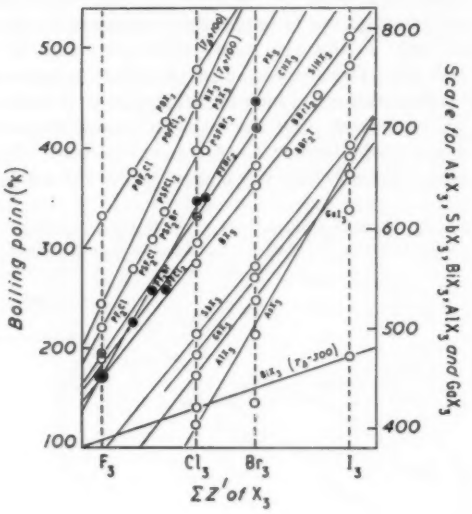


FIG. 11.

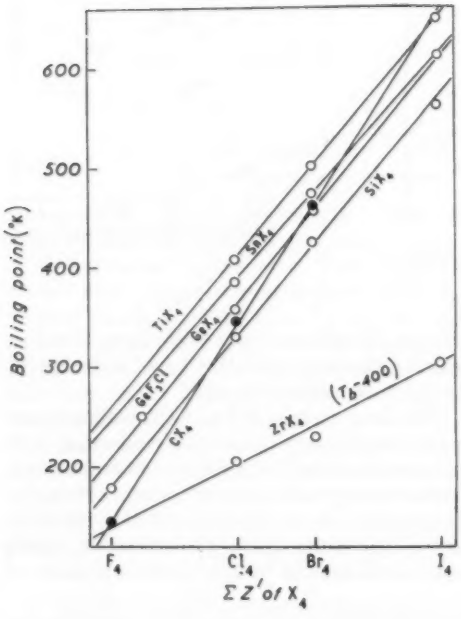


FIG. 9. *Boiling point of* BeX_2, $SiMe_2X_2$, CH_2X_2, *sym-*$C_2H_4X_2$, *and* HgX_2 versus *the sum of the effective atomic numbers of the* X_2 *part.*

FIG. 10. *Boiling point of* POX_3, NX_3, PSX_3, PX_3, CHX_3, $SiHX_3$, BX_3, SbX_3, GaX_3, AlX_3, AsX_3, *and* BiX_3 versus *the sum of the effective atomic numbers of the* X_3 *part.*

FIG. 11. *Boiling point of* TiX_4, SnX_4, GeX_4, SiX_4, CX_4, *and* ZrX_4 versus *the sum of the effective atomic numbers of the* X_4 *part.*

approximate ones, but they illustrate unmistakably the existence of a definite trend, occasional departure, especially in fluorine compounds, being not uncommon. However, the slight departure from linearity with FCl and ICl may be due to a small percentage of ionic character in the bond.

Boiling Points of Halides of the Type RX_2.—Fig. 9 shows the boiling points of various dihalides of this type. In all cases (except HgF_2 and BeF_2 which are ionic) fairly good straight lines are obtained. It is remarkable that Be and Hg, which form predominantly covalent halides, behave normally whereas Cd and Zn (not shown), which form ionic halides, behave anomalously.

Boiling Points of the Halides of the Type RX_3.—The trihalides of B, Al, Ga, N, P, As, Sb, Bi, CH, SiH, PO, and PS obey our equation fairly closely (Fig. 10). The metals and metalloids, however, show occasional anomalies, particularly their fluorides, and this is ascribed to the fact that they are either polar or associated, or tend to decompose on boiling.

Boiling Points of the Halides of the Type RX_4.—For the boiling points of tetrahalides plotted against Z', Fig. 11 shows that each sequence gives a straight line. The diagram for silicon tetrahalides has already been published.[1] The boiling points of the titanium tetrafluoride and stannic fluoride are, however, too high for our equations, presumably owing to association or polarity. The boiling point of zirconium tetrafluoride is not available.

Discussion.—We have established the existence of definite trends in the boiling point of halogen compounds, a ready explanation of which is, however, not available. As we believe, however, that the attractive force at the surface of all halogen atoms is the same,

TABLE 1. *Boiling points of halides* (°K).

Sequence of halides	X = F	X = Cl	X = Br	X = I	*a*	*b*
X_2	85·16 (85·00)	238·56 (237·00)	331·94 (332·00)	457·57 (S) (484·00)	9·50	−86·00
HX	292·56 (158·03)	188·16 (188·19)	207·16[d] (207·04)	237·76 (237·20)	3·77	124·10
CH_3X	195·16 (199·09)	249·46 (245·01)	277·76 (273·71)	315·76 (319·63)	5·74	147·40
C_6H_5X	359·16 (362·03)	405·26 (401·42)	429·36 (426·04)	461·76 (465·43)	4·92	124·20
$Si(CH_3)_3X$	289·56[a] (288·53)	330·16[a] (329·09)	353·16[a] (354·44)	— (395·00)	5·07	242·90
$Si(C_2H_5)_3X$	383·16[a] (382·08)	416·66[a] (417·44)	439·66[a] (439·54)	— (474·90)	4·42	342·30
CH_2X_2	221·56[b] (222·66)	313·26 (311·78)	370·96 (367·48)	453·16(D) (456·60)	5·57	122·40
$Si(CH_3)_2X_2$	275·86[a] (275·86)	343·36[a] (343·38)	385·46[a] (385·58)	— (453·10)	4·22	199·90
s-$C_2H_4X_2$	248·46[c] (248·14)	330·46 (330·22)	383·16 (381·52)	452·16 (463·60)	5·13	155·80
HgX_2	923·16 (543·72)	577·16 (575·56)	595·16 (595·46)	627·16 (627·30)	1·99	507·90
BeX_2	— (692·82)	761·16[d] (757·32)	793·16[c] (797·62)	863·16[c] (862·10)	4·03	620·30
BX_3	172·16 (146·20)	285·66 (280·60)	363·76 (364·60)	483·16 (499·00)	5·61	− 5·00
AlX_3	1564·16[d] (S) (325·51)	453·16[d] (S) (451·03)	528·16[d] (529·48)	655·16 (655·00)	5·23	184·30
GaX_3	— (385·42)	474·36[d] (480·46)	552·16[d] (539·86)	629·16[d] (634·90)	3·96	278·50
NX_3	144·16[d] (144·16)	344·16[d] (344·08)	— (469·03)	— (668·95)	8·33	−80·75
PX_3	172·16[d] (165·65)	347·86[d] (337·25)	446·06 (444·50)	— (616·10)	7·15	−27·40
AsX_3	— (225·77)	403·36[c] (396·41)	494·16[c] (503·06)	676·16 (673·70)	7·11	33·80
SbX_3	592·16[d] (375·09)	494·16[d] (491·97)	561·16[d] (569·79)	683·16(Ca) (686·67)	4·87	243·60
BiX_3	— (678·52)	720·16 (713·56)	726·16 (735·46)	773·16(D) (770·50)	1·46	639·10
CHX_3	190·96[c] (189·64)	334·36 (334·12)	423·56 (424·44)	— (568·92)	6·02	27·10
$SiHX_3$	192·96 (192·43)	306·16 (307·39)	382·16 (379·24)	493·16 (494·20)	4·79	63·10
$Si(CH_3)X_3$	242·96[a] (240·28)	339·36[a] (342·04)	406·66[a] (405·64)	— (507·40)	4·24	125·80
POX_3	233·36[c] (230·50)	378·46[c] (376·90)	466·16 (468·40)	— (614·80)	6·10	65·80
PSX_3	220·26[d] (220·25)	398·16 (399·05)	448·16(D) (510·80)	— (689·60)	7·45	19·10
CX_4	145·16[c] (146·58)	349·96 (341·46)	462·66 (463·26)	— (658·14)	6·09	−72·70
SiX_4	178·16[d] (178·00)	330·73 (330·00)	426·16 (425·00)	563·16 (577·00)	4·75	− 7·0
GeX_4	236·76[d] (206·40)	359·66 (368·00)	459·66 (469·00)	648·16 (630·60)	5·05	24·60
SnX_4	978·16 (246·48)	387·26 (386·64)	475·16 (474·24)	613·16 (614·40)	4·38	88·80
TiX_4	557·16 (261·94)	409·56 (410·42)	503·16 (503·22)	650·36[d] (651·70)	4·64	94·90
ZrX_4	— (534·62)	604·16[d] (598·46)	630·16[d] (638·36)	704·16[d] (702·20)	2·66	462·80

For references, see Table 2, on following page.

the boiling point, which measures the total intermolecular force, increases linearly with the area of the halogen atoms in similar molecules. We are in favour of such a simple explanation because Z'/R_c^2 is constant [2] for all halogens and since Z' appears to be the net nuclear charge, *i.e.*, nuclear charge operating outside an atom after partial screening by the

electron cloud, Z'/R_c^2 is the net electrical force at the surface of a halogen atom, and so this force becomes equal for all halogen atoms. This equality being assumed, the above explanation fits well with the facts and also explains why the rate of increase in boiling point is approximately the same for all types of halide.

All boiling-point data for the halides used are collected in Tables 1 and 2 and their

TABLE 2. *Boiling points of halides* (°K).

Type RX_4

SiX_4	F_3Cl	216·16[d] (216·00)	F_2Cl_2	254·16[d] (254·00)	FCl_3	292·16[d] (292·00)
	F_3Br	231·46[a] (239·75)	F_2Br_2	286·86[a] (301·50)	FBr_3	356·96[a] (363·25)
	Cl_3Br	353·16 (353·75)	Cl_2Br_2	377·16 (377·50)	$ClBr_3$	401·16[d] (401·25)
	Cl_3I	386·56 (391·75)	Cl_2I_2	445·16 (453·50)	ClI_3	508·16 (515·25)
	Br_3I	465·16 (463·00)	Br_2I_2	503·16 (501·00)	BrI_3	528·16 (539·00)
	FCl_3Br	308·56[a] (315·75)	$FClBr_2$	333·66[a] (339·50)		
CX_4	F_3Cl	193·16[b] (195·26)	F_2Cl_2	245·16[b] (243·98)	FCl_3	297·26[b] (292·70)
	F_3Br	— (225·71)	F_2Br_2	298·16 (281·02)	FBr_3	380·16 (384·05)
	Cl_3Br	377·26 (371·87)	Cl_2Br_2	408·16 (402·32)	$ClBr_3$	433·16 (432·77)
	Cl_3I	415·16 (420·59)	Cl_2I_2	— (499·76)	ClI_3	— (578·93)
GeX_4	F_3Cl	252·86[c] (246·80)	F_2Cl_2	270·36[d] (287·20)	FCl_3	310·66[c] (327·60)

Type RX_3

PX_3	F_2Cl	225·86[d] (222·85)	F_2Br	258·06[d] (258·40)	FCl_2	259·31[d] (280·05)	FBr_2	351·56[d] (351·55)
POX_3	F_2Cl	276·46[d] (279·30)	Cl_2Br	410·76 (407·40)	FCl_2	326·06[d] (328·10)	$ClBr_2$	438·16(Ca) (437·90)
PSX_3	F_2Cl	279·46[d] (279·85)	F_2Br	308·66[d] (307·10)	FCl_2	337·86[d] (339·45)	FBr_2	398·46[d] (403·95)
BX_3	Br_2I	398·16[c] (409·40)	BrI_2	453·16[c] (454·20)				
$Si(CH_3)X_3$	F_2Cl	272·66[a] (274·20)	FCl_2	302·66[a] (308·12)				

Type X_2

X_2	FCl	172·36[c] (161·00)	ICl	370·56[c] (360·50)	ClBr	278·16[d] (284·00)	IBr	389·16[c] (408·00)

D, Decomposes; S, Sublimes; Ca, Calculated.

All boiling-point data are taken from the International Critical Tables unless otherwise indicated. [a] Post, "Silicones and Other Organic Silicon Compounds," Reinhold Publishing Corporation, New York, 1949. [b] Bigelow, *Chem. Rev.*, 1947, **40**, 51. [c] Hodgman, "Handbook of Physics and Chemistry," Chemical Rubber Publishing Co., Ohio, 1949. [d] Sidgwick, "Chemical Elements and Their Compounds," Vols. I and II, Clarendon Press, Oxford, 1950. [e] Landolt–Börnstein Tabellen.

sources indicated. We have also calculated the boiling points on the basis of Somayajulu's equation (eqn. 1) and presented the calculated values in parentheses for each compound. The calculated values seldom differ much from the observed values except for the highly associated fluorides. It being remembered that the compounds considered are not usually purely covalent, but partially ionic in some cases, the agreement reached without the consideration of the dipole–dipole interactions and other factors is remarkable.

We have also recorded the slopes and intercepts of eqn. (1) for all the above sequences in Table 1. Since the ratio R_c^2/Z' is a constant, 0·5845 Å^2, for halogens, the constant a' in eqn. (2) can be obtained by multiplying a by 0·5845.

One remarkable feature of the slope a is that it continually increases with the period number of R in RX_n; for example among the sequences BeX_2, BX_3, CX_4, NX_3, and X_2 it is 4·0, 5·6, 6·1, 8·3, and 9·5 respectively. The slope decreases with increase in atomic number of R in any group. These observations indicate that the electronegativity of the elements and period number are important factors in determining the boiling point.

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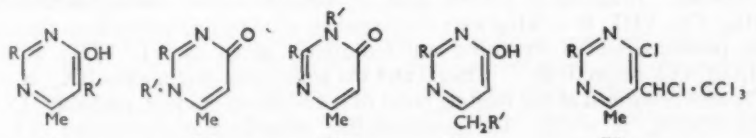
976. *Pyrimidines. Part II.* The Synthesis and Some Reactions of Pyrimidine-5-aldehydes.*

By R. Hull.

Some 4-hydroxypyrimidines react with chloral to give 4-hydroxy-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidines which can be hydrolysed to 4-hydroxypyrimidine-5-aldehydes. The Reimer–Tiemann aldehyde synthesis has also been applied to some 4-hydroxypyrimidines. Pyrimidines, containing electron-releasing groups, are described in which the above reactions either failed or gave other products. Some reactions of 2-amino-4-hydroxy-6-methylpyrimidine-5-aldehydes are also reported.

Pyrimidine-aldehydes have been previously suggested as a fruitful field for biological investigation, but possibly owing to the difficulty of synthesis no extensive work on them has been reported.

Pyrimidine-4-aldehydes have been prepared by Johnson and his co-workers [1] from aliphatic intermediates, and by Japanese workers [2] by ozonolysis of styrylpyrimidines. King and King [3] obtained a derivative of a pyrimidine-2-aldehyde after nitrosation of 4 : 6-dihydroxy-2-methylpyrimidine. Delépine [4] reported the formation of 4-amino-2-methylpyrimidine-5-aldehyde on reduction of the corresponding 5-cyanopyrimidine, and Price, May, and Pickel,[5] using McFadyen and Stevens's method,[6] converted the same cyano-compound into the 5-aldehyde. A derivative of 5-formylbarbituric acid has been



(I) (II) (III) (IV) (V)

synthesised by Ridi and Papini [7] from barbituric acid and diphenylformamidine. The present paper describes two methods [8] for the preparation of pyrimidine-5-aldehydes.

Method I.—Reaction of chloral with tertiary arylamines [9] and with phenols [10] yields addition products which decompose on alkaline hydrolysis to amino- and hydroxy-aldehydes respectively. It has now been found that a similar reaction takes place between chloral and some 4-hydroxypyrimidines. Reaction of chloral with 4-hydroxy-6-methyl-2-piperidinopyrimidine (I; R = piperidino, R′ = H) could yield, theoretically, four products [I—IV; R = piperidino, R′ = $CH(OH)\cdot CCl_3$] because chloral reacts with amides [11] and with activated methyl groups attached to heterocyclic rings.[12] The product

* Part I, *J.*, 1956, 2033.

[1] Johnson and Cretcher, *J. Amer. Chem. Soc.*, 1915, **37**, 2144; Johnson and Cretcher, *J. Biol. Chem.* 1916, **26**, 99; Johnson and Mikeska, *J. Amer. Chem. Soc.*, 1919, **41**, 810; Johnson, *ibid.*, 1929, **51**, 1274; Johnson and Schroeder, *ibid.*, 1931, **53**, 1989.

[2] Kondo and Yanai, *J. Pharm. Soc. Japan*, 1937, **57**, 747; Ochiai and Yanai, *ibid.*, 1938, **58**, 397.

[3] King and King, *J.*, 1947, 943.

[4] Delépine, *Compt. rend.*, 1938, **206**, 865; *Bull. Soc. chim. France*, 1938, **5**, 1539; Delépine and Jensen, *ibid.*, 1939, **6**, 1663.

[5] Price, May, and Pickel, *J. Amer. Chem. Soc.*, 1940, **62**, 2818.

[6] McFadyen and Stevens, *J.*, 1936, 584.

[7] Ridi and Papini, *Gazzetta*, 1946, **76**, 376.

[8] B.P. specifn. 741,667.

[9] Panly and Schanz, *Ber.*, 1923, **56**, 979; G.P. 475,918, 598,652; F.P. 791,818; Valvet and Mejuto, *Anales Fis. Quim.*, 1936, **34**, 641; Meldrum and Lonkar, *J. Univ. Bombay*, 1937, **6**, 116; Balfe and Webber, *J.*, 1942, 718.

[10] Boessneck, *Ber.*, 1885, **18**, 1516; 1886, **19**, 365; Knofler and Boessneck, *ibid.*, 1887, **20**, 3193; G.P. 61,551; Ettel and Weichet, *Coll. Czech. Chem. Comm.*, 1949, **14**, 747.

[11] Chattaway and James, *J.*, 1943, 109.

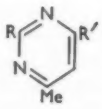
[12] Einhorn, *Ber.*, 1886, **19**, 904; *Annalen*, 1891, **265**, 208; Ettel, Weichet, and Chyba, *Coll. Czech. Chem. Comm.*, 1950, **15**, 528.

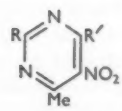
XUM

was soluble in alkali. The nitropyrimidine (I; R = piperidino, R′ = NO_2) did not react with chloral: formulæ (II—IV) may therefore be discounted. Subsequent alkaline hydrolysis of the product thus shown to have structure [I; R = piperidino, R′ = $CH(OH)\cdot CCl_3$] gave 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde in good yield. Reactions of the compound are described below; they are typical of aromatic aldehydes, and are in agreement with the structure proposed.

Chloral was caused to react with other pyrimidines (I; R = NH_2, NHMe, or NMe_2, R′ = H), and the addition products [R′ = $CH(OH)\cdot CCl_3$] were hydrolysed to the aldehydes (R′ = CHO). In most cases it was advantageous, in the addition reaction, to add pyridine as a solvent and possible catalyst. Attempted purification of the amino-compound [I; R = NH_2, R′ = $CH(OH)\cdot CCl_3$] by dissolution in cold aqueous alkali with subsequent reprecipitation by acid gave a substance $C_7H_9O_3N_3Cl_2$, indicating a formula [I; R = NH_2, R′ = $CH(OH)\cdot CCl_2\cdot OH$ or R′ = CH—CCl_2,H_2O]).

(VI); R = N<[CH2]5
(VII); R′ = Cl
(VIII); R′ = SMe

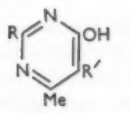




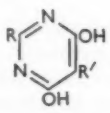
(IX)

Treatment of the piperidino-compound [I; R′ = $CH(OH)\cdot CCl_3$] with phosphoryl chloride gave the pentahalogenated derivative (V).

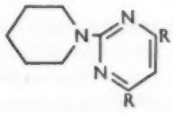
"Abnormal" Reactions of Chloral with Pyrimidines.—The aminopyrimidines (VI; R′ = NH_2; VII, VIII; R = NH_2) were recovered on alkaline hydrolysis from their chloral addition products, whose structures are tentatively given as [VI—VIII; R′ = R = $NH\cdot CH(OH)\cdot CCl_3$ respectively]. Chloral and the aminochloropyrimidine (IX; R = NH_2, R′ = Cl) were re-formed at the melting point of the addition product, probably [IX; R = $NH\cdot CH(OH)\cdot CCl_3$, R′ = Cl]. The corresponding aminohydroxypyrimidine (IX; R =



(X)



(XI)



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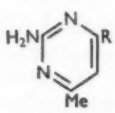
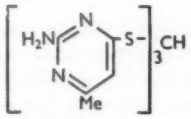


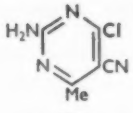
(XIII)



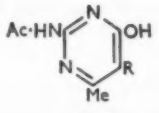
(XIV)

NH_2, R′ = OH) did not react with chloral. The addition products [X and XI; R = $CH_2\cdot CH(OH)\cdot CCl_3$, R′ = $CH(OH)\cdot CCl_3$] which resulted from the corresponding hydroxy-methylpyrimidines (X and XI; R = Me, R′ = H) with chloral gave, on hydrolysis, water-soluble products from which no pyrimidine-aldehydes could be isolated. The activity of the 2-methyl group was further exemplified by the addition product [XI; R = $CH_2\cdot CH(OH)\cdot CCl_3$, R′ = NO_2] which was obtained from the 2-methyl-5-nitro-pyrimidine (XI; R = Me, R′ = NO_2) and chloral.

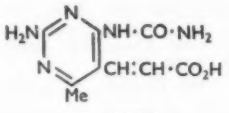
The addition product [XI; R = Ph, R′ = $CH(OH)\cdot CCl_3$], obtained from the hydroxy-



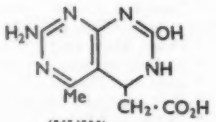
(XV)



(XVI)



(XVII)



(XVIII)

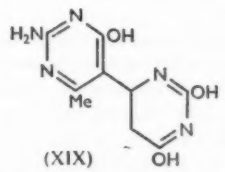
phenylpyrimidine (XI; R = Ph, R′ = H) and chloral, gave, on hydrolysis, an unidentified acid $C_{13}H_{10}O_4N_2$, which failed to react with dinitrophenylhydrazine.

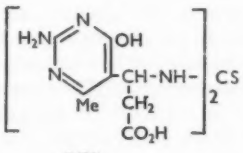
It was not possible to isolate addition products from the pyrimidines (XII; R = H or Me) and chloral.

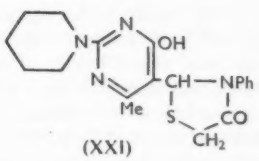
Method II.—The Reimer–Tiemann synthesis of phenolic aldehydes has now been successfully applied to a number of hydroxypyrimidines: the hydroxypyrimidines (I; R = NH_2, NHMe, or NMe_2, R′ = H), (X; R = OH, R′ = H), and (XI; R = piperidino or Ph, R′ = H) gave the corresponding pyrimidine-aldehydes (R′ = CHO).

The behaviour of pyrimidines having other electron-releasing groups was then investigated. The aminopyrimidines (XIII; R = NH_2 or SMe) did not yield aldehydes; the analogous mercapto-compound gave the trisubstituted methane (XIV); thiophenol and its *p*-chloro- and *p*-methyl derivative [13] undergo a similar type of reaction.

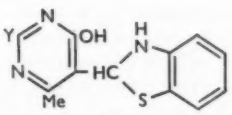
Some Reactions of 2-Amino-4-hydroxy-6-methylpyrimidine-5-aldehyde (I; R = NH_2, R′ = CHO).—This compound gave the usual ketonic derivatives and with permanganate yielded the 5-carboxylic acid. Attempts to prepare the 4-chloropyrimidine by treatment with phosphoryl chloride failed, as did experiments using the 2-acetamido-aldehyde.[14] However, the aldehyde oxime reacted normally with phosphoryl chloride and yielded the chloro-nitrile (XV). Dehydration of the oxime was also effected by acetic anhydride, which gave the nitrile (XVI; R = CN).

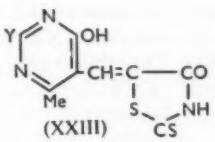

(XIX)

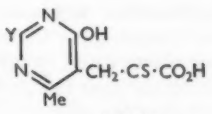

(XX)

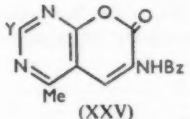

(XXI)

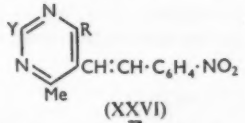
Possibly because of the insolubility of the aldehyde in common organic solvents, attempts to synthesise the pyrimidylacrylic acid by condensation with malonic acid were unsuccessful. Urea has been suggested as a versatile solvent.[15] With urea as " solvent," and under Knoevenagel conditions, a compound $C_9H_{11}O_3N_5$ was obtained. Potentiometric analysis indicated three acidic centres and absence of a true carboxylic group. If

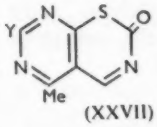

(XXII)

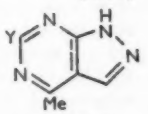

(XXIII)

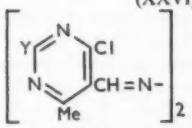

(XXIV)

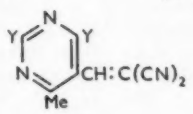

(XXV)


(XXVI)


(XXVII)


(XXVIII)


(XXIX)


(XXX)

Y = piperidino

the acrylic acid had been formed as an intermediate, formulæ (XVII—XIX) are possible for the product of its reaction with urea. Since cinnamic acid with urea yields the 4 : 5-dihydro-2 : 6-hydroxy-4-phenylpyrimidine, the analogous structure (XIX) seems the most probable. The other two possibilities (XVII and XVIII) may be excluded since they

[13] Gabriel, *Ber.*, 1877, **10**, 185.
[14] Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.
[15] Clark, *Nature*, 1951, **168**, 876.

XUM

both contain a carboxyl group, and, in a further experiment, 2-amino-4-hydroxy-6-methylpyrimidine (I; R = NH_2, R′ = H) was recovered unchanged under similar reaction conditions with urea.

Treatment of the aldehyde (I; R = NH_2, R′ = CHO) with malonic acid and thiourea gave an acid, believed to have structure (XX).

Some Reactions of 4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde* (I; R = piperidino, R′ = CHO).—Treatment of this aldehyde with aniline, *NN*-dimethyl-*p*-phenylenediamine, hydroxylamine, (methylthio)thiocarbonylhydrazine,[17] and thiosemicarbazide readily yielded the expected products, and hydrazine gave the azine.

The Schiff base formed with aniline was converted by reaction with thioglycollic acid [18] into the thiazolidone (XXI), and with nitromethane (unlike benzylideneaniline which gave a bimolecular product [19]) it gave the 5-nitrovinylpyrimidine identical with the product obtained directly from the aldehyde and nitromethane.

The chloro-nitrile analogous to (XV) was obtained, either by treatment of the oxime with phosphoryl chloride, or by dehydration of the oxime with acetic anhydride to the hydroxy-nitrile (cf. XVI) followed by treatment with phosphoryl chloride. Hydrolysis of the hydroxy-nitrile with sulphuric acid at 100° gave the amide.

With acetophenone and malonic acid the aldehyde gave the chalcone and the pyrimid-5-ylacrylic acid respectively. Condensation with *o*-aminothiophenol was also smooth and gave the thiazoline (XXII). The product (XXIII), obtained by reaction with rhodanine, gave, on alkaline hydrolysis, the acid (XXIV). Hippuric acid yielded the expected azlactone, attempted hydrolysis of which with hot dilute sodium hydroxide solution gave, on acidification, an isomeric colourless compound believed to be the lactone (XXV). *p*-Nitrophenylacetic acid afforded the nitrostilbene (XXVI; R = OH) which was converted *via* the chloropyrimidine (XXVI; R = Cl) into the amine (XXVI; R = NH_2).

Conversion of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde into a compound containing a second reactive group was accomplished by conversion of the 4-hydroxyl group into a chloro-substituent by treatment with phosphoryl chloride in the cold. Treatment of this chloro-aldehyde with thiourea gave the thiazone (XXVII), with elimination of ammonia. Replacement of chlorine and condensation took place with hydrazine hydrate which gave the tetra-azaindene (XXVIII); hydrazine sulphate, however, yielded the chloro-azine (XXIX). The chloro-aldehyde with malononitrile under Knoevenagel conditions gave the dinitrile (XXX), replacement of the chlorine atom taking place with the catalyst (piperidine). Replacement of the chlorine atom, with retention of the aldehyde group, took place with piperidine alone, which yielded 4-methyl-2 : 6-dipiperidinopyrimidine-5-aldehyde; with potassium thiocyanate it gave the thiocyanato-, and with methanethiol the methylthio-pyrimidine subsequent treatment of which with hydrazine gave the azine.

Experimental

4-*Hydroxy*-6-*methyl*-2-*piperidino*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—(*a*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine (116·5 g.), chloral (98·5 g.), and pyridine (91 ml.) were heated on a steam-bath during 2 hr. Next morning, the crude *product* [153 g.; m. p. 218° (decomp.)] obtained by the addition of water gave colourless needles, m. p. 230° (decomp.), from 2-ethoxyethanol (Found: C, 42·5; H, 4·55; N, 12·25. $C_{12}H_{16}O_2N_3Cl_3$ requires C, 42·3; H, 4·7; N, 12·3%). (*b*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine (1·7 g.) and chloral (3 ml.) were heated with stirring on a steam-bath during 15 min. Water was added to the cooled mixture, and the crude product (2·6 g.) collected. The product, identical with the above, crystallised from 2-ethoxyethanol.

4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde*.—Potassium hydroxide (154 g.) in

[16] Fisher and Roeder, *Ber.*, 1901, **34**, 3762; Evans and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 5001.
[17] Busch, *J. prakt. Chem.*, 1916, **93**, 60.
[18] Surrey, *J. Amer. Chem. Soc.*, 1947, **69**, 2911; 1948, **70**, 4262.
[19] Hurd and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4813.

water (100 ml.) and alcohol (700 ml.) was added to a suspension of 4-hydroxy-6-methyl-2-piperidino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (100 g.) in warm alcohol (1·1 l.). The mixture was heated on a steam-bath for 30 min. and the potassium derivative which had separated was collected and dissolved in water (4 l.). The solution was filtered from a small quantity of insoluble material, and the *aldehyde* (55 g.) was precipitated by acetic acid. It crystallised from alcohol in pale yellow plates, m. p. 235° (Found: C, 59·6; H, 6·9; N, 18·65. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8; N, 19·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol in orange needles, m. p. >300° (Found: C, 50·95; H, 4·75; N, 23·8. $C_{17}H_{19}O_5N_7$ requires C, 50·9; H, 4·75; N, 24·4%).

2-*Dimethylamino*-4-*hydroxy*-6-*methyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—A mixture of 2-dimethylamino-4-hydroxy-6-methylpyrimidine (2·9 g.), chloral (3·1 g.), and pyridine (3 ml.) was heated on a steam-bath during 2 hr. and worked up in the usual manner. Recrystallisation of the crude material (6·0 g.) from 2-ethoxyethanol gave the *product* as colourless needles, m. p. 221—222° (decomp.) (Found: C, 36·0; H, 4·1; N, 14·15. $C_9H_{12}O_2N_3Cl_3$ requires C, 35·95; H, 4·0; N, 14·0%).

2-*Dimethylamino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (3·85 g.) in water (2·5 ml.) and alcohol (18 ml.) was added to a suspension of 2-dimethylamino-4-hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (2·1 g.) in warm alcohol (28 ml.). Working up by the usual procedure gave the *aldehyde* (1·2 g.) which crystallised from 2-ethoxyethanol as colourless needles, m. p. >300° (Found: C, 53·55; H, 6·25; N, 23·2. $C_8H_{11}O_2N_3$ requires C, 53·05; H, 6·1; N, 23·2%).

4-*Hydroxy*-6-*methyl*-2-*methylamino*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 4-hydroxy-6-methyl-2-methylaminopyrimidine (2·78 g.), chloral (3·25 g.) and pyridine (3·0 ml.), the *compound* (4·4 g.) crystallised from aqueous 2-ethoxyethanol in colourless plates, m. p. 202° (decomp.) (Found: C, 33·9; H, 3·5; N, 14·4. $C_8H_{10}O_2N_3Cl_3$ requires C, 33·5; H, 3·5; N, 14·6%).

4-*Hydroxy*-6-*methyl*-2-*methylaminopyrimidine*-5-*aldehyde*.—4-Hydroxy-6-methyl-2-methylamino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (2·86 g.) in warm alcohol (20 ml.) was added to potassium hydroxide (2·8 g.) in water (10 ml.) and alcohol (15 ml.), and heated on a steam-bath for 2 hr. Excess of reagent was removed under diminished pressure, the residue dissolved in water (20 ml.) and filtered from insoluble material, and the *aldehyde* (0·95 g.) precipitated by acetic acid. It crystallised from 2-ethoxyethanol in colourless needles, m. p. 290° (decomp.) (Found: C, 50·6; H, 5·6; N, 25·5. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·2%).

2-*Amino*-4-*hydroxy*-6-*methyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 2-amino-4-hydroxy-6-methylpyrimidine (5·0 g.), chloral (6·5 g.), and pyridine (8·0 ml.), the *compound* [8·2 g.; m. p. 185—190° (decomp.)] crystallised from aqueous 2-ethoxyethanol in colourless prismatic needles, m. p. 192—194° (decomp.) (Found: N, 15·2; Cl, 39·3. $C_7H_8O_2N_3Cl_3$ requires N, 15·4; Cl, 39·1%). The crude product was dissolved in alkali and extracted with ether. Addition of acetic acid precipitated a *substance* which dried as an amorphous powder, m. p. >300° (Found: N, 16·95; Cl, 28·55. $C_7H_9O_3N_3Cl_2$ requires N, 16·6; Cl, 28·05%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (38·5 g.) in water (25 ml.) was diluted with alcohol (180 ml.) and added to a slurry of 2-amino-4-hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (20 g.) in warm alcohol (280 ml.) and heated on a steam-bath for 2 hr. The solid was collected and combined with the residue left after evaporation of the solvent from the filtrate. The combined solids were treated with warm water (150 ml.), filtered from insoluble material, and acidified to pH 6 with hydrochloric acid. The *compound* (12 g.; m. p. 263°) was collected and purified from a small quantity of water. It dried as a pale yellow amorphous powder, m. p. 269—270° (decomp.) (Found: C, 44·65; H, 5·5; N, 25·65. $C_6H_7O_2N_3,0{\cdot}5H_2O$ requires C, 44·4; H, 5·0; N, 25·9%).

The semicarbazone hydrochloride (see below) had m. p. 242° (decomp.), undepressed on admixture with the semicarbazone hydrochloride prepared from the aldehyde obtained by the Reimer–Tiemann method.

4-*Chloro*-6-*methyl*-2-*piperidino*-5-(1 : 2 : 2 : 2-*tetrachloroethyl*)*pyrimidine*.—4-Hydroxy-6-methyl-2-piperidino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (4·4 g.) was heated at 100° with phosphoryl chloride (20 ml.) during 10 min. and next morning added to ice. The precipitate (2·75 g.) was collected and washed with water. Crystallisation from alcohol gave

the *product* as colourless prismatic needles, m. p. 115° (Found: C, 38·35; H, 3·85; Cl, 48·0. $C_{12}H_{14}N_2Cl_8$ requires C, 38·15; H, 3·7; Cl, 47·05%).

4-Amino-6-methyl-2-piperidinopyrimidine.—4-Chloro-6-methyl-2-piperidinopyrimidine [20] (50 g.) was heated in an autoclave with alcoholic ammonia (1 l., saturated at 10°) at 150° during 14 hr. After evaporation the resulting mixture was treated with sodium hydroxide and ether-extracted, and the extract evaporated. The residue (20 g.; m. p. 129°), after being washed with light petroleum, crystallised from benzene–light petroleum (b. p. 60—80°) and gave the *aminopyrimidine* as colourless prisms, m. p. 137—138° (Found: C, 62·8; H, 8·75; N, 28·65. $C_{10}H_{16}N_4$ requires C, 62·5; H, 8·35; N, 29·15%).

6-Methyl-2-piperidino-4-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—Prepared from the above aminopyrimidine (0·85 g.), chloral (0·78 g.), and pyridine (1·0 ml.) the *compound* (1·25 g.) crystallised from benzene in colourless prisms, m. p. 147—148° (Found: N, 16·05; Cl, 31·8. $C_{12}H_{17}ON_4Cl_3$ requires N, 16·5; Cl, 31·4%).

Potassium hydroxide (0·92 g.) in water (0·6 ml.) and alcohol (5 ml.) was added to a hot solution of this product (0·6 g.) in alcohol (4·2 ml.) and the whole heated on a steam-bath for 10 min. The mixture was evaporated under diminished pressure and the residue extracted with hot benzene, then evaporated to a small volume, and light petroleum was added. The compound was collected and was crystallised from aqueous alcohol, to give 4-amino-6-methyl-2-piperidinopyrimidine, m. p. 132° (Found: C, 62·5; H, 8·2; N, 28·5. Calc. for $C_{10}H_{16}N_4$: C, 62·5; H, 8·35; N, 29·15%).

4-Chloro-6-methyl-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—2-Amino-4-chloro-6-methylpyrimidine (2·0 g.) and chloral (6·0 ml.) were heated together on a steam-bath during 2 hr., then cooled; water was added and the solid (3·9 g.) collected and washed with water. Recrystallisation from alcohol gave the *product* as colourless prismatic needles, m. p. 160—161° (Found: C, 29·1; H, 3·0; Cl, 49·1. $C_7H_7ON_3Cl_4$ requires C, 28·9; H, 2·4; Cl, 48·8%).

Potassium hydroxide (0·385 g.) in water (0·5 ml.) and alcohol (5 ml.) was added to a suspension of this product (1·0 g.) in alcohol (20 ml.). A solution was formed from which colourless needles (0·65 g.) of 2-amino-4-chloro-6-methylpyrimidine were precipitated (m. p. and mixed m. p. 182°).

4-Methyl-6-methylthio-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—Prepared from 2-amino-4-methyl-6-methylthiopyrimidine [21] (1·0 g.) and chloral (2·0 ml.), the *compound* (1·9 g.) crystallised from aqueous methanol as colourless prisms, m. p. 150—152° (Found: C, 32·3; H, 3·2; N, 13·8; Cl, 36·2. $C_8H_{10}ON_3Cl_3S$ requires C, 31·75; H, 3·3; N, 13·9; Cl, 35·2%).

This product (1·75 g.) was heated with potassium hydroxide (0·65 g.) in water (0·5 ml.) and alcohol (15 ml.) on a steam-bath for 20 min. After evaporation to dryness and washing with water the solid (0·7 g.) gave, on crystallisation from methanol, 2-amino-4-methyl-6-methylthiopyrimidine as light brown hexagonal prisms, m. p. 155° (Found: C, 46·3; H, 5·6; N, 27·6. Calc. for $C_6H_9N_3S$: C, 46·45; H, 5·8; N, 27·1%).

Reaction of Chloral with 2-Amino-4-chloro-6-methyl-5-nitropyrimidine.—A mixture of chloral (11 ml.) and 2-amino-4-chloro-6-methyl-5-nitropyrimidine (5·6 g.) was heated on a steam-bath during 2 hr., cooled, and treated with water. After 2 days the solid was collected. Crystallisation from aqueous alcohol (carbon) gave the product (4·2 g.) as colourless prismatic needles (Found: Cl, 41·5. $C_7H_6O_3N_4Cl_4$ requires Cl, 42·25%). The substance, which was probably *4-chloro-6-methyl-5-nitro-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine*, melted and resolidified at 130°, giving off chloral, finally melting at 219° alone or mixed with 2-amino-4-chloro-6-methyl-5-nitropyrimidine.

4-Hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)-pyrimidine.—4-Hydroxy-2 : 6-dimethylpyrimidine [22] (10·0 g.), chloral (15·0 g.), and pyridine (10 ml.) were caused to react and worked up in the usual way. The *product* (6·6 g.) was purified for analysis by dissolution in 2-ethoxyethanol, filtration, and addition of water to incipient precipitation, which gave a colourless amorphous powder, m. p. 177° (decomp.) (Found: C, 28·6; H, 2·55; N, 6·85; Cl, 50·8. $C_{10}H_{10}O_3N_2Cl_6$ requires C, 28·65; H, 2·4; N, 6·7; Cl, 50·8%).

4 : 6-Dihydroxy-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyrimidine.—Pyridine (8·0 ml.) was added slowly to 4 : 6-dihydroxy-2-methylpyrimidine (2·5 g.)

[20] Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357.
[21] Backer and Grevenstuk, *Rec. Trav. chim.*, 1942, **61**, 291.
[22] Pinner, *Ber.*, 1889, **22**, 1616.

and chloral (6·5 g.), and the mixture was heated on a water-bath for 3 hr. Water was added to the cooled mixture. After 7 days, the solid (4·1 g.) was collected. Purification by extraction with hot alcohol and addition of water to incipient precipitation gave the *product*, which dried as a light brown amorphous powder, m. p. >300° (Found: N, 7·1; Cl, 48·8. $C_9H_8O_4N_2Cl_6$ requires N, 6·7; Cl, 50·6%).

4 : 6-*Dihydroxy*-5-*nitro*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*pyrimidine*.—4 : 6-Dihydroxy-2-methyl-5-nitropyrimidine [23] (1·7 g.), chloral (1·77 g.), and pyridine (3·0 ml.) were heated on a steam-bath during 2 hr., then cooled. Water was added and the solution was decanted from a little unchanged starting material. 5N-Sodium hydroxide (4 ml.) was added, and the solution was extracted with ether. The aqueous layer was acidified with hydrochloric acid (cooling), and, after 2 days, the solid (1·8 g.) was collected. The *pyrimidine* [m. p. 205—210° (decomp.) (inserted at 200°)] was obtained as light brown prismatic needles by adding boiling water to an alcoholic extract of the crude product (Found: C, 25·5; H, 2·45; N, 12·35. $C_7H_6O_5N_3Cl_3,H_2O$ requires C, 25·0; H, 2·4; N, 12·5%).

4 : 6-*Dihydroxy*-2-*phenyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 4 : 6-dihydroxy-2-phenylpyrimidine [24] (12·25 g.), chloral (10·65 g.), and pyridine (15 ml.), the *compound* (3·4 g.) separated from 2-ethoxyethanol and water, and dried as a light cream amorphous powder, m. p. >300° (Found: C, 43·4; H, 2·85; N, 8·3. $C_{12}H_9O_3N_2Cl_3$ requires C, 42·95; H, 2·7; N, 8·35%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (805 g.) was dissolved in water (960 ml.), and one-fifth of this solution was added to a suspension of 2-amino-4-hydroxy-6-methylpyrimidine (300 g.) in alcohol (1·2 l.) in a bath at 80° with good stirring. The remainder of the potassium hydroxide solution and chloroform (286 ml.) were then added simultaneously during 4 hr. The bath was lowered during this addition, the heat of reaction being sufficient to maintain gentle reflux. After overnight stirring and cooling, the solid was collected, washed with alcohol, and dissolved in warm water (2·5 l.). The solution was filtered from a little insoluble material, and 5N-hydrochloric acid added to pH 10, followed by acetic acid to pH 6. The crude product (140 g.) crystallised from water as pale yellow prismatic needles, m. p. >300° (Found: C, 41·8; H, 5·0; N, 24·7. Calc. for $C_6H_7O_2N_3,H_2O$: C, 42·1; H, 5·25; N, 24·55%. Loss *in vacuo* at 130°; 11·1%. Calc. for the monohydrate, 10·5%). The *hydrochloride* (m. p. >300°) was obtained by dissolving the base in the minimum quantity of warm 5N-hydrochloric acid, then quickly cooling and scratching the mixture. The solid was collected and washed with acetone (Found: Cl, 17·3. $C_6H_7O_2N_3,HCl,H_2O$ requires Cl, 17·1%).

2-*Dimethylamino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Chloroform (3·82 g.) was added slowly to a stirred mixture of potassium hydroxide (8·4 g.) and 2-dimethylamino-4-hydroxy-6-methylpyrimidine (3·06 g.) in alcohol (10 ml.) and water (10 ml.) at 80°. The mixture was then refluxed during 1 hr. and cooled. Next morning the solid (mainly inorganic material) was collected and the filtrate evaporated to dryness. The residue was dissolved in water (25 ml.) and filtered, and the product (1·0 g.) was precipitated with acetic acid. It crystallised from 2-ethoxyethanol as colourless needles, m. p. >300° (Found: C, 53·4; H, 6·1; N, 23·9. Calc. for $C_8H_{11}O_2N_3$: C, 53·05; H, 6·1; N, 23·2%).

4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde*.—Chloroform (2·55 ml.) was added to a stirred mixture of sodium hydroxide (5·6 g.) and 4-hydroxy-6-methyl-2-piperidinopyrimidine (3·86 g.) in 2-ethoxyethanol (15 ml.) and water (15 ml.) at 80°. Working up by the usual procedure gave the aldehyde (0·8 g.) which crystallised from aqueous ethanol as pale yellow needles, m. p. 230—232°, undepressed on admixture with the aldehyde obtained by the chloral reaction (Found: C, 60·0; H, 6·6; N, 18·9. Calc. for $C_{11}H_{15}O_2N_3$: C, 59·7; H, 6·8; N, 19·0%).

2 : 4-*Dihydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Chloroform (8·95 g.), and potassium hydroxide (14 g.) in water (15 ml.) were added simultaneously to a stirred suspension of 2 : 4-dihydroxy-6-methylpyrimidine (6·3 g.) in potassium hydroxide (2·8 g.) and water (25 ml.) and alcohol (20 ml.) at 80° during 15 min. After 1 hour's stirring under reflux the mixture was cooled and filtered and the filtrate evaporated to dryness. The residue was dissolved in water and acidified to litmus with 5N-hydrochloric acid, no solid being precipitated. The aldehyde could be isolated as the *phenylhydrazone*, which was purified from dimethylformamide as a pale cream powder, m. p. >300° (Found: C, 58·6; H, 5·3; N, 23·2. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·9; N, 22·95%), as the 2 : 4-*dinitrophenylhydrazone*, which was purified by dissolution in

[23] Huber and Holscher, *Ber.*, 1938, **71**, 94.
[24] Pinner, *Ber.*, 1908, **41**, 3517.

hot dimethylformamide and addition of water to incipient precipitation and obtained as an orange-red powder, m. p. >300° (Found: C, 42·7; H, 2·9; N, 24·3. $C_{12}H_{10}O_6N_6$ requires C, 43·1; H, 3·0; N, 25·1%), or as the *semicarbazone*, which was purified by solution in dilute alkali and reprecipitation with hydrochloric acid and obtained as a pale cream powder, m. p. 289° (decomp.) (Found: C, 38·1; H, 4·6. $C_7H_9O_3N_5,0·5H_2O$ requires C, 38·2; H, 4·55%).

4 : 6-*Dihydroxy*-2-*piperidinopyrimidine*-5-*aldehyde*.—Chloroform (16·8 g.), and potassium hydroxide (26·5 g.) in water (28 ml.) were added simultaneously to 4 : 6-dihydroxy-2-piperidinopyrimidine (20 g.) and potassium hydroxide (5·3 g.) in alcohol (40 ml.) and water (8 ml.) at 80° during 30 min., then allowed to reflux for a further hour, cooled, and filtered, and the filtrate was evaporated to dryness. The combined solids were dissolved in water (320 ml.) and filtered, and the *product* (8·1 g.) precipitated by the addition of 5N-hydrochloric acid to pH 6. From 7 : 3 propan-2-ol–water it formed orange crystals, m. p. >300° (sintering at 290°) (Found: N, 19·4. $C_{10}H_{13}O_3N_3$ requires N, 18·85%). The 2 : 4-*dinitrophenylhydrazone* was obtained as an orange amorphous powder, m. p. 294° (decomp.) (Found: N, 24·7. $C_{16}H_{17}O_6N_7$ requires N, 24·3%).

4 : 6-*Dihydroxy*-2-*phenylpyrimidine*-5-*aldehyde*.—Prepared from 4 : 6-dihydroxy-2-phenylpyrimidine (3·76 g.), the crude *product* [2·5 g.; m. p. 286—287° (decomp.)] was obtained as a pale cream powder (Found: C, 60·1; H, 4·3; N, 13·0. $C_{11}H_8O_3N_2,0·25H_2O$ requires C, 59·85; H, 3·85; N, 12·7%).

Tri-(2-*amino*-4-*methyl*-6-*pyrimidylthio*)*methane*.—Chloroform (5·75 g.) was added slowly to a stirred solution of 2-amino-4-mercapto-6-methylpyrimidine [25] (4·2 g.) and potassium hydroxide (6·35 g.) in alcohol (10 ml.) and water (10 ml.) at 80°. After a further 1 hr. the precipitate was collected and washed with water, then dissolved in alcohol; addition of water to incipient precipitation gave the crude product, which after a second similar purification gave *tri*-(2-*amino*-4-*methyl*-6-*pyrimidylthio*)*methane* (2·85 g.) as a cream amorphous powder, m. p. 217—218° (Found: C, 44·1; H, 4·6; S, 22·3. $C_{16}H_{19}N_9S_3$ requires C, 44·3; H, 4·4; S, 22·2%).

Tri-p-*tolyl Trithio*-*orthoformate*.—Chloroform (11·5 g.) was added slowly to *p*-tolylthiophenol (6·2 g.) and potassium hydroxide (12·7 g.) in alcohol (19 ml.) and water (19 ml.) at 80°. After a further 1 hr., the mixture was cooled, water (100 ml.) was added, and the oil was extracted with ether (3 × 100 ml.). The combined extracts were washed with water and dried, and the ether was removed. The residual *thio*-*orthoformate* (7·4 g.) crystallised from light petroleum as needles, m. p. 111° (Found: C, 69·0; H, 6·1; S, 25·2. $C_{22}H_{22}S_3$ requires C, 69·1; H, 5·8; S, 25·1%).

Tri-p-*chlorophenyl Trithio*-*orthoformate*.—This was prepared as described above, but with *p*-chlorothiophenol (7·25 g.). The *thio*-*orthoformate* (8·7 g.) crystallised from light petroleum in prismatic needles, m. p. 111—112° (Found: S, 21·5; Cl, 24·25. $C_{19}H_{13}S_3Cl_3$ requires S, 21·65; Cl, 24·0%).

Compounds from 2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Semicarbazide hydrochloride (3·35 g.) in water (22·5 ml.) was added to the aldehyde (4·25 g.) in warm 5N-hydrochloric acid (27·5 ml.). The *semicarbazone hydrochloride* (6·25 g. crude) crystallised from aqueous alcohol containing a few drops of 5N-hydrochloric acid as needles, m. p. 240° (decomp.) (Found: C, 34·0; H, 4·8; N, 34·3; Cl, 14·0. $C_7H_{10}O_2N_6,HCl$ requires C, 34·1; H, 4·45; N, 34·1; Cl, 14·4%). Acetic acid precipitated the *semicarbazone* from alkaline solution which dried as an amorphous powder, m. p. 280—283° (decomp.) (Found: C, 36·8; H, 5·5. $C_7H_{10}O_2N_6,H_2O$ requires C, 36·8; H, 5·3%).

The *thiosemicarbazone dihydrochloride* [6·3 g. from 4·25 g.; m. p. 235° (decomp.)] (Found: Cl, 23·8. $C_7H_{10}ON_6S,2HCl$ requires Cl, 23·9%) dissociated on attempted recrystallisation from water. Addition of ammonium chloride to a solution of the solid in N-sodium hydroxide gave the *thiosemicarbazone*, m. p. 255—256° (decomp.) (Found: C, 33·1; H, 5·1; N, 32·5. $C_7H_{10}ON_6S,1·5H_2O$ requires C, 33·2; H, 5·15; N, 33·2%).

The aldehyde (3·4 g.) in 5N-sulphuric acid (8 ml.) was added to hydrazine sulphate (8·1 g.) in water (100 ml.). The yellow *azine sulphate* (3·6 g.) was collected and after being washed with hot water and alcohol had m. p. 273—274° (decomp.) (Found: C, 33·6; H, 4·3; N, 25·7. $C_{12}H_{14}O_2N_8,H_2SO_4,2H_2O$ requires C, 33·05; H, 4·6; N, 25·7%). The *azine hydrochloride* (3·1 g.), prepared similarly from the aldehyde (3·06 g.) and hydrazine hydrochloride, had m. p. 270° (decomp.) (Found: C, 38·0; H, 5·0; N, 29·3. $C_{12}H_{14}O_2N_8,2HCl$ requires C, 38·4; H, 4·25; N, 29·85%).

The aldehyde (50 g.) in warm 5N-hydrochloric acid (300 ml.) and hydroxylamine

[25] Gabriel and Cohen, *Ber.*, 1899, **32**, 2926.

hydrochloride (41·25 g.) in warm water (90 ml.) were mixed. The following morning the *oxime hydrochloride* (34·7 g.) was crystallised from water, giving needles, m. p. 225° (decomp.) (Found: C, 34·7; H, 4·3; Cl, 16·8. $C_6H_8O_2N_4$,HCl requires C, 35·2; H, 4·4; Cl, 17·35%). Repeated recrystallisation of the hydrochloride from water gave the *oxime* as prisms, m. p. >300° (Found: C, 41·8; H, 5·0; N, 31·8. $C_6H_8O_2N_4$,0·25H_2O requires C, 41·7; H, 4·9; N, 32·4%).

The aldehyde (6·4 g.) in 5N-hydrochloric acid (21 ml.) with *o*-hydroxybenzhydrazide [16] (5·7 g.) in 5N-hydrochloric acid (38 ml.) gave the yellow N'-*o*-*hydroxybenzoylhydrazone dihydrochloride* (8·0 g.) which, washed with water and alcohol, had m. p. >300° (Found: C, 42·9; H, 5·0; N, 19·6. $C_{13}H_{13}O_3N_5$,2HCl requires C, 43·35; H, 4·2; N, 19·45%).

4-(2-*Acetamido*-4-*hydroxy*-6-*methyl*-5-*pyrimidylmethylidene*)-5-*oxo*-2-*phenyloxazoline*.—The aldehyde (1·7 g.), hippuric acid (1·8 g.) and fused sodium acetate (0·8 g.) were heated under reflux in acetic acid (5·0 ml.) and acetic anhydride (4·0 ml.) during 5 min. After storage, the yellow solid (0·95 g.) was collected. It crystallised from 2-ethoxyethanol, to give the *azlactone* as pale yellow needles, m. p. 281—283° (Found: C, 59·8; H, 4·3; N, 15·9. $C_{17}H_{14}O_4N_4$ requires C, 60·35; H, 4·15; N, 16·55%).

(2-*Amino*-4-*hydroxy*-6-*methyl*-5-*pyrimidylmethylidene*)*rhodanine*.—A mixture of the aldehyde (1·53 g.), rhodanine (1·33 g.), fused sodium acetate (2·4 g.), and acetic acid (25 ml.) was heated under reflux for 1 hr. The *rhodanine derivative* (2·15 g.) was collected and washed with water and alcohol; it crystallised from aqueous dimethylformamide as yellow prismatic needles, m. p. >300° (Found: C, 40·8; H, 3·5; N, 21·1. $C_9H_8O_2N_4S_2$ requires C, 40·3; H, 3·0; N, 20·9%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*carboxylic Acid*.—Potassium permanganate (1·05 g.) in water (15 ml.) was added with shaking to a warm solution of the aldehyde (1·71 g.) in 5N-sodium hydroxide (2·0 ml.) and water (10 ml.). After 5 min. the mixture was filtered and the filtrates were adjusted to pH 5 with 5N-hydrochloric acid. The *acid* (1·0 g.) was collected; it crystallised from water as colourless prismatic needles, m. p. 245—246° (decomp.) (Found: C, 42·7; H, 4·2; N, 24·5. $C_6H_7O_3N_3$ requires C, 42·6; H, 4·15; N, 24·85%).

2-*Amino*-4-*chloro*-5-*cyano*-6-*methylpyrimidine*.—Dimethylaniline (3·9 ml.) was added slowly to 2-amino-4-hydroxy-6-methylpyrimidine-5-aldoxime hydrochloride (6·5 g.) and phosphoryl chloride (39 ml.) and the whole heated under reflux for 20 mins. The cooled mixture was added to ice-water, and aqueous ammonia added to alkalinity to Brilliant Yellow. The *chlorocyanopyrimidine* (3·6 g.) was collected. It crystallised from alcohol as colourless prisms, m. p. 258—259° (decomp.) (inserted at 240°) (Found: N, 33·5; Cl, 21·05. $C_6H_5N_4Cl$ requires N, 33·25; Cl, 21·05%).

2-*Acetamido*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—2-Amino-4-hydroxy-6-methylpyrimidine-5-aldehyde (1·5 g.) and acetic anhydride (40 ml.) were heated under reflux for 2 hr. After 2 days the solid (7·2 g.) was collected and washed with ethyl acetate. Recrystallisation from aqueous alcohol gave the *acetyl derivative* as light brown prisms, m. p. 240° (decomp.) (Found: C, 49·2; H, 4·8; N, 21·3. $C_8H_9O_3N_3$ requires C, 49·2; H, 4·6; N, 21·55%).

2-*Acetamido*-5-*cyano*-4-*hydroxy*-6-*methylpyrimidine*.—2-Amino-4-hydroxy-6-methylpyrimidine-5-aldoxime hydrochloride (6·8 g.) and acetic anhydride (40 ml.) were heated under reflux for 1 hr. The *cyanopyrimidine* was collected and washed with alcohol. It crystallised from aqueous 2-ethoxyethanol as light brown needles (2·35 g.), m. p. 285—286° (Found: C, 49·6; H, 3·8; N, 28·6. $C_8H_6O_2N_4$ requires C, 50·0; H, 4·15; N, 29·15%).

2-*Amino*-5-(5 : 6-*dihydro*-2 : 4-*dihydroxy*-6-*pyrimidyl*)-4-*hydroxy*-6-*methylpyrimidine*.—A mixture of the aldehyde (1·7 g.), malonic acid (1·15 g.), urea (3 g.), and γ-picoline (1·0 ml.) was heated with stirring at 130—135° during 30 min., then cooled. Water was added to the resin and the mixture was set aside. The solid (1·25 g.) was later collected. Purification from water gave the *product* as yellow crystals, m. p. >300° (Found: C, 45·6; H, 5·2; N, 29·5. $C_9H_{11}O_3N_5$ requires C, 45·6; H, 4·65; N, 29·5%). It dissolved in aqueous sodium carbonate or hydrochloric acid. It was insoluble in cold aqueous sodium hydrogen carbonate. It did not form a derivative with 2 : 4-dinitrophenylhydrazine.

Reaction of 2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde with Malonic Acid and Thiourea*.—A mixture of the aldehyde (1·7 g.), malonic acid (1·15 g.), thiourea (3·0 g.), and γ-picoline (1·0 ml.) was heated with stirring at 150° during 20 min., then cooled and treated with water. After standing overnight the solid was collected. It was purified from water as a light yellow amorphous powder. The product, believed to be NN'-*di*-[1-(2-*amino*-4-*hydroxy*-6-*methyl*-5-*pyrimidyl*)-2-*carboxyethyl*]*thiourea*, had m. p. >300° (Found: C, 44·3; H, 5·2; N,

[16] Struve and Radenhausen, *J. prakt. Chem.*, 1895, **52**, 239.

25·3; S, 5·7. $C_{17}H_{22}O_6N_6S$ requires C, 43·8; H, 4·7; N, 24·1; S, 6·85%). It dissolved in excess of aqueous sodium hydrogen carbonate. It did not form a 2 : 4-dinitrophenylhydrazone.

4-Hydroxy-6-methyl-5-phenyliminomethyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (22 g.) and freshly distilled aniline (10·2 g.) were heated together at 100° for 15 min. Crystallisation of the melt from aqueous alcohol gave the *anil* as feathery yellow needles (27·9 g.), m. p. 110—112° (Found: C, 65·25; H, 7·1; N, 17·6. $C_{17}H_{20}ON_4,H_2O$ requires C, 65·0; H, 7·0; N, 17·8%).

5-p-Dimethylaminophenylimino-4-hydroxy-6-methyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·1 g.) and *NN*-dimethyl-*p*-phenylenediamine (0·68 g.) were ground together and heated at 180° during 5 min. The mixture was extracted with alcohol, and water added to incipient precipitation. Crystallisation of the solid from ethyl acetate gave the *anil* as red prisms, m. p. 171—172° (Found: C, 68·05; H, 7·9; N, 20·85. $C_{19}H_{25}ON_5$ requires C, 67·3; H, 7·4; N, 20·65%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime.—A solution of hydroxylamine hydrochloride (14 g.) and sodium acetate (28 g.) in water (45 ml.) was added to a suspension of the aldehyde (22 g.) in alcohol (300 ml.), and the mixture was heated under reflux during 5 hr. The solid (26 g.) was collected. Recrystallisation from 2-ethoxyethanol gave the *oxime* as colourless needles, m. p. 240° (decomp.) (Found: C, 55·4; H, 6·75; N, 23·85. $C_{11}H_{16}O_2N_4$ requires C, 55·9; H, 6·8; N, 23·75%).

N'-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene)-N'-[(methylthio)carbonylthio]-hydrazine.—(Methylthio)thiocarbonylhydrazine [17] (1·3 g.) in methanol (7 ml.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) in dioxan (60 ml.). Next morning the *product* (2·25 g.) was collected. It crystallised from methanol as yellow prisms, m. p. 216—217° (decomp.) (Found: C, 48·45; H, 5·5; N, 20·8. $C_{13}H_{19}ON_5S_2$ requires C, 48·0; H, 5·8; N, 21·5%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde Thiosemicarbazone.—Thiosemicarbazide (0·55 g.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·1 g.) in 2-ethoxyethanol and quickly heated to the b. p. to effect dissolution, then cooled to 100° and kept at this temperature for 30 min. The *product* (1·2 g.) crystallised on cooling. It recrystallised from acetic acid as light buff prismatic needles, m. p. >300° (Found: C, 49·3; H, 6·15; S, 10·4. $C_{12}H_{18}ON_6S$ requires C, 49·0; H, 6·1; S, 10·9%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldazine.—Hydrazine hydrate (65% w/v, 5 g.) in 2-ethoxyethanol (50 ml.) was added to a solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (11 g.) in 2-ethoxyethanol (100 ml.), and the mixture was kept at 100° for 2 hr. The *azine* (8·0 g.) was precipitated on cooling. It was purified from dimethylformamide as a yellow amorphous powder, m. p. 307° (decomp.) (Found: C, 60·0; H, 6·95; N, 25·7. $C_{22}H_{30}O_2N_8$ requires C, 60·25; H, 6·85; N, 25·6%).

2-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl)-4-oxo-3-phenylthiazolidine.—4-Hydroxy-6-methyl-5-phenylimino-2-piperidinopyrimidine (2·97 g.) and 90% mercaptoacetic acid (1·02 g.) in benzene (40 ml.) were heated under a Dean and Stark receiver during 30 min. Excess of reagent was removed under diminished pressure. The residue, washed with aqueous sodium hydrogen carbonate and twice recrystallised from alcohol, gave the *product* (1·5 g.) as orange-yellow prisms, m. p. 272—274° (inserted at 250°) (Found: C, 57·35; H, 6·3; N, 14·85. $C_{19}H_{22}O_2N_4S,1·5H_2O$ requires C, 57·4; H, 6·3; N, 14·1%).

4-Hydroxy-6-methyl-5-2'-nitrovinyl-2-piperidinopyrimidine.—(*a*) 4-Hydroxy-6-methyl-5-phenylimino-2-piperidinopyrimidine (1·6 g.) and nitromethane (0·54 ml.) in alcohol (5 ml.) were heated under reflux during 2 hr. After cooling, the solid (1·15 g.) was collected and washed with alcohol. The filtrates gave a positive test for a primary arylamine. Recrystallisation from 2-ethoxyethanol gave the *product* as orange-yellow prismatic needles, m. p. 282° (decomp.) (Found: C, 54·95; H, 6·25; N, 21·05. $C_{12}H_{16}O_3N_4$ requires C, 54·55; H, 6·05; N, 21·2%). (*b*) Nitromethane (0·8 ml.) was added to a warm solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) in 2-ethoxyethanol (15 ml.) and piperidine (0·1 ml.). Next morning the precipitate (2·2 g.) was collected. Recrystallisation from 2-ethoxyethanol gave the nitrovinylpyrimidine, m. p. 279—280° (decomp.), identical with the above (Found: C, 54·85; H, 6·35%).

5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime (1·2 g.) and acetic anhydride (10 ml.) were heated under reflux during 2 hr., cooled and poured on ice. Next morning the solid (0·8 g.) was collected. Crystallisation

from 2-ethoxyethanol gave the *cyanopyrimidine* as colourless needles, m. p. 292—294° (Found: C, 60·6; H, 6·5; N, 25·85. $C_{11}H_{14}ON_4$ requires C, 60·55; H, 6·4; N, 25·7%).

4-Chloro-5-cyano-6-methyl-2-piperidinopyrimidine.—(*a*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime (2·9 g.) was heated under reflux with phosphoryl chloride (12 ml.) during 1 hr. The mixture was cooled and decomposed with ice. The solid (2·75 g.; m. p. 126—127°) was collected. Crystallisation from alcohol gave the *chlorocyanopyrimidine* as colourless plates, m. p. 133—134° (Found: C, 55·75; H, 5·6; N, 23·35. $C_{11}H_{13}N_4Cl$ requires C, 55·8; H, 5·5; N, 23·65%). (*b*) 5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine (2·2 g.) was heated under reflux with phosphoryl chloride (10 ml.) during 15 min. and worked up as above, giving the chlorocyanopyrimidine as colourless prisms, m. p. 131·5—132·5°, identical with the above.

5-Carbamoyl-4-hydroxy-6-methyl-2-piperidinopyrimidine.—5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine (0·22 g.) and concentrated sulphuric acid (2·5 ml.) were heated together at 100° during 1½ hr., then kept for 2 days. Excess of acid was reduced with 5N-sodium hydroxide and finally removed with sodium acetate, and the solid (0·3 g.) collected. Recrystallisation from 2-ethoxyethanol gave the *amide* as colourless prismatic needles, m. p. 290° (decomp.) (Found: C, 56·15; H, 6·85; N, 23·3. $C_{11}H_{16}O_2N_4$ requires C, 55·95; H, 6·8; N, 23·7%).

5-(2-Benzoylvinyl)-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), acetophenone (1·2 g.), and sodium hydroxide (0·8 g.) in water (40 ml.) and alcohol (1 ml.) was set aside, with occasional shaking, during 7 days. The orange-red solid (1·1 g.) was collected, suspended in water, and acidified with acetic acid. Crystallisation of the resulting solid (1·0 g.) from 2-ethoxyethanol gave the *chalcone* as pale yellow needles, m. p. 256° (Found: C, 70·8; H, 6·65; N, 13·5. $C_{19}H_{21}O_2N_3$ requires C, 70·6; H, 6·5; N, 13·0%).

5-2′-Carboxyvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), malonic acid (1·05 g.), and piperidine (5·0 ml.) was warmed, with stirring, to a homogeneous melt, then set aside overnight, diluted with water (15 ml.), and acidified, and the precipitate collected. Purification, by dissolution of the crude product in dilute aqueous ammonia followed by acidification, gave the *pyrimidylacrylic acid* (1·3 g.) as a yellow amorphous powder, m. p. 231° (decomp.) (Found: C, 58·95; H, 6·75; N, 15·7. $C_{13}H_{17}O_3N_3$ requires C, 59·3; H, 6·45; N, 15·95%).

2-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl)benzothiazoline.—Dimethylaniline (1·2 g.) was added to a stirred mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) and *o*-aminothiophenol hydrochloride (1·6 g.) in alcohol (50 ml.), and the whole was heated under reflux for 30 min. Water (100 ml.) was added to the solution. Dissolution of the precipitate (4 g.) in 5N-hydrochloric acid and then basification with ammonia gave a solid. Extraction with hot butanol gave the *product* as an orange-red amorphous powder, m. p. 212—213° (decomp.) (inserted at 200°) (Found: C, 62·15; H, 6·1; N, 17·0. $C_{17}H_{20}ON_4S$ requires C, 62·2; H, 6·1; N, 17·05%).

(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene)rhodanine.—Fused sodium acetate (2·4 g.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) and rhodanine (1·3 g.) in acetic acid (15 ml.) and the whole was heated, with stirring, on a steam-bath during 30 min. After cooling, the orange-yellow solid (2·0 g.) was collected and washed with water. Crystallisation from 2-ethoxyethanol–propan-2-ol gave the *rhodanine derivative acetate* as dark orange prismatic needles, m. p. 315—316° (decomp.) (Found: C, 48·15; H, 5·2; N, 14·5; S, 16·7. $C_{14}H_{16}O_2N_4S_2,C_2H_4O_2$ requires C, 48·5; H, 5·05; N, 14·15; S, 16·2%).

5-(2-Carboxy-2-thionoethyl)-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 11N-sodium hydroxide (11·75 ml.), water (15 ml.), and the foregoing acetate (10 g.) was heated on a steam-bath during 30 min., then diluted with water (80 ml.), filtered, cooled, and acidified quickly with 5N-acetic acid. The yellow solid (7·8 g.) was collected and washed with water. Purification from hot methanol with addition of water to incipient precipitation gave the *acid* as an amorphous yellow powder, m. p. 182—183° (decomp.) (Found: C, 53·5; H, 6·0; N, 14·8. $C_{13}H_{17}O_3N_3S$ requires C, 52·9; H, 5·75; N, 14·25%).

4-[4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene]-5-oxo-2-phenyloxazoline.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), hippuric acid (1·8 g.), fused sodium acetate (0·8 g.), acetic anhydride (4·0 ml.), and acetic acid (5·0 ml.) was heated under reflux during 5 min., then kept for 2 days. The yellow precipitate (1·8 g.) was collected

and washed with alcohol. Recrystallisation from 2-ethoxyethanol gave the *product* as yellow needles, m. p. 215—217° (Found: C, 65·85; H, 5·4; N, 14·8. $C_{20}H_{20}O_3N_4$ requires C, 65·95; H, 5·5; N, 15·4%).

α-*Benzamido*-β-(4-*hydroxy*-6-*methyl*-2-*piperidino*-5-*pyrimidyl*)*acrylic Lactone*.—A mixture of the above oxazoline (1·2 g.), 0·5N-sodium hydroxide (13·2 ml.), and alcohol (20 ml.) was heated under reflux during 20 min. Excess of reagent was removed under diminished pressure at 40°. The volume was adjusted to 50 ml. with water and the whole acidified with acetic acid. The precipitate (1·2 g.) was collected and washed with water. Crystallisation from 2-ethoxyethanol gave the *lactone* as colourless needles, m. p. 205° (Found: C, 65·95; H, 5·7; N, 15·75. $C_{20}H_{20}O_3N_4$ requires C, 65·95; H, 5·5; N, 15·4%).

4-*Hydroxy*-6-*methyl*-5-4′-*nitrostyryl*-2-*piperidinopyrimidine*.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), *p*-nitrophenylacetic acid (1·85 g.), and piperidine (7·5 ml.) was heated with stirring at 150—160° during 3 hr. After cooling, the mixture was acidified with dilute acetic acid, and the solid (2·05 g.) was collected, and washed with water, sodium hydrogen carbonate solution, and alcohol. Crystallisation from 2-ethoxyethanol gave the *styrylpyrimidine* as red needles, m. p. 310° (Found: C, 62·3; H, 6·0; N, 15·9. $C_{18}H_{20}O_3N_4,0·5H_2O$ requires C, 61·9; H, 6·0; N, 16·05%).

4-*Chloro*-6-*methyl*-5-4′-*nitrostyryl*-2-*piperidinopyrimidine*.—4-Hydroxy-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine (17 g.) was heated under reflux with phosphoryl chloride (100 ml.) during 20 min. The whole was cooled and decomposed by ice. The yellow precipitate was collected and washed with water. Crystallisation from 2-ethoxyethanol gave the *chloropyrimidine* (13·1 g.) as yellow needles, m. p. 164—165° (Found: C, 59·9; H, 5·6; N, 16·15. $C_{18}H_{19}O_2N_4Cl$ requires C, 60·25; H, 5·3; N, 15·65%).

4-*Amino*-6-*methyl*-5-4′-*nitrostyryl*-2-*piperidinopyrimidine*.—4-Chloro-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine (27 g.) was heated in an autoclave with alcoholic ammonia (1 l. saturated at 0°) at 125° during 10 hr. The *aminopyrimidine* (22·3 g.) was collected. After recrystallisation from alcohol it had m. p. 217—218° (Found: C, 63·5; H, 6·2; N, 20·65. $C_{18}H_{21}O_2N_5$ requires C, 63·7; H, 6·2; N, 20·65%).

4-*Chloro*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde*.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (10 g.) was added slowly to phosphoryl chloride (50 ml.) with shaking and cooling. The following morning the mixture was poured on ice and extracted with ether, and the extract washed with sodium hydrogen carbonate solution, dried, and evaporated. The oil (11·3 g.) gradually crystallised. Recrystallisation from aqueous alcohol gave the *chloropyrimidine* as colourless needles, m. p. 91—92° (Found: C, 55·8; H, 5·45; N, 17·4. $C_{11}H_{14}ON_3Cl$ requires C, 55·1; H, 5·85; N, 17·55%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol in crimson red prismatic needles, m. p. 259—260° (decomp.) (Found: C, 48·25; H, 4·4; N, 23·0. $C_{17}H_{15}O_4N_7Cl$ requires C, 48·6; H, 4·3; N, 23·35%).

5-*Methyl*-2-*oxo*-7-*piperidino*-2H-1-*thia*-3 : 6 : 8-*triazanaphthalene*.—4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (6·5 g.), thiourea (2·26 g.), alcohol (30 ml.), and water (25 ml.) were heated under reflux during 45 min., then kept for 2 days, diluted with water, and neutralised with sodium hydrogen carbonate solution. The *product* (6·7 g.) was collected. When purified from aqueous alcohol it was obtained as an amorphous yellow powder, m. p. 228—230° (decomp.) (inserted 220°) (Found: C, 54·3; H, 6·1; N, 21·0; S, 13·0. $C_{12}H_{14}ON_4S$ requires C, 54·95; H, 5·35; N, 21·4; S, 12·2%).

4-*Methyl*-6-*piperidino*-1 : 2 : 5 : 7-*tetra*-*azaindene*.—A solution of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·2 g.) in warm alcohol (10 ml.) was added to hydrazine hydrate (75% w/v; 3·8 g.) in alcohol (5 ml.) and kept for 2 days. The solid (0·95 g.) was collected. Recrystallisation from alcohol gave the *product* as prismatic needles, m. p. 209—210° (Found: C, 60·3; H, 6·6; N, 32·3. $C_{11}H_{18}N_6$ requires C, 60·8; H, 6·9; N, 32·25%).

4-*Chloro*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldazine*.—Hydrazine sulphate (0·09 g.) in water (1 ml.) was added to a hot solution of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (0·24 g.) in alcohol (7 ml.). Immediate precipitation took place. After 30 minutes' heating on the steam-bath the product (0·24 g.) was collected and washed with alcohol. Recrystallisation from 2-ethoxyethanol gave the *azine* as pale yellow needles, m. p. 256° (decomp.) (Found: C, 55·9; H, 6·4; N, 23·55. $C_{22}H_{28}N_8Cl_2$ requires C, 55·6; H, 5·9; N, 23·55%).

5-(2 : 2-*Dicyanovinyl*)-4-*methyl*-2 : 6-*dipiperidinopyrimidine*.—Piperidine (4·0 ml.) was added to a solution of malononitrile (1·06 g.) and 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (4·8 g.) in hot alcohol (12 ml.) and the mixture was heated under reflux during 30 min. After

cooling, the solid was collected. Recrystallisation from alcohol gave the *product* (3·1 g.) as yellow prismatic needles, m. p. 196° (Found: C, 67·85; H, 7·2; N, 25·2. $C_{13}H_{24}N_6$ requires C, 67·85; H, 7·15; N, 25·0%).

4-Methyl-2 : 6-dipiperidinopyrimidine-5-aldehyde.—Piperidine (0·2 ml.), 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (0·24 g.), and alcohol (7 ml.) were heated under reflux during 30 min., then cooled, and the solid (0·15 g.) collected. Recrystallisation from aqueous alcohol gave *4-methyl-2 : 6-dipiperidinopyrimidine-5-aldehyde* as pale yellow prisms, m. p. 117° (Found: C, 66·1; H, 7·8; N, 19·5. $C_{16}H_{24}ON_4$ requires C, 66·65; H, 8·3; N, 19·45%).

4-Methyl-2-piperidino-6-thiocyanatopyrimidine-5-aldehyde.—4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·4 g.), potassium thiocyanate (1·49 g.), water (25 ml.), and alcohol (25 ml.) were heated under reflux during 3 hr. After cooling, the product with a little unchanged starting material was collected. Two recrystallisations from aqueous alcohol gave the *thiocyanatopyrimidine* as needles, m. p. 172° (Found: C, 54·7; H, 5·4; N, 21·7. $C_{12}H_{14}ON_4S$ requires C, 54·95; H, 5·3; N, 21·4%).

4-Methyl-6-methylthio-2-piperidinopyrimidine-5-aldehyde.—11N-Sodium hydroxide (6·0 ml.) was added with rapid stirring to mixed solutions of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·4 g.) in hot alcohol (20 ml.) and *S*-methyl*iso*thiuronium sulphate (2·61 g.) in hot water (9 ml.), and the whole was kept at 50—60° during 30 min. The mixture was cooled and the *methylthiopyrimidine* (2·6 g.) collected. Recrystallisation from alcohol gave pale yellow needles, m. p. 126—127° (Found: C, 57·4; H, 6·3; N, 16·25. $C_{12}H_{17}ON_3S$ requires C, 57·35; H, 6·8; N, 16·75%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol as red needles, m. p. 284—285° (decomp.) (Found: C, 50·25; H, 4·8; N, 22·7. $C_{18}H_{21}O_4N_7S$ requires C, 50·1; H, 4·85; N, 22·75%).

4-Methyl-6-methylthio-2-piperidinopyrimidine-5-aldazine.—5N-Hydrochloric acid (2·0 ml.) was added to a warm solution of 4-methyl-6-methylthio-2-piperidinopyrimidine-5-aldehyde (0·25 g.) and hydrazine hydrate (75% w/v; 0·7 g.) in alcohol (4 ml.). After 1 hr. the solid (0·29 g.) was collected, then extracted with dilute sodium hydroxide and refiltered. Recrystallisation from 2-ethoxyethanol gave the *azine* as fine yellow needles, m. p. 275—276° (Found: C, 57·8; H, 6·6; N, 22·4. $C_{24}H_{34}N_8S_2$ requires C, 57·8; H, 6·85; N, 22·5%).

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977. *Studies on* Aspergillus niger. *Part VIII.* The Purification of Glucamylase.*

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The purification is described of an enzyme, glucamylase, which yields glucose as the sole product of its action on amylose and, when analysed on a paper chromatogram, shows only one component that exhibits amylolytic activity. Its optimum pH is 4·0 and optimum temperature 52°; the minimum concentration of acetate buffer necessary for full activity is 0·02M.

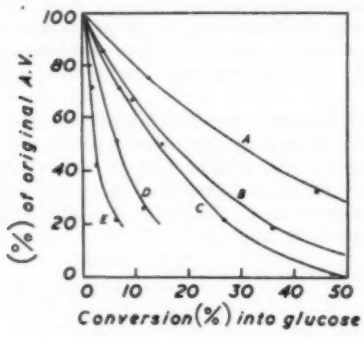
THE existence of starch-degrading enzymes in *Aspergillus niger* has long been known, but considerable confusion has arisen in the nomenclature of the amylases from various *Aspergillus* species and other moulds. The principal amylase-type enzyme produced by moulds is an α-amylase, sometimes called a dextrinising enzyme. The deviations from the expected behaviour of an α-amylase by mould-enzyme preparations have usually been attributed to contamination with other enzymes such as β-amylase, maltase, and a saccharifying or glucogenic enzyme. In a study of the amylolytic enzymes of a number of moulds, especially of the *Aspergillus* and *Rhizopus* species, Corman and Langlykke [1] found that while in some cases there was a rapid liquefaction of starch solution with the production

* Part VII, *J.*, 1957, 3541.

[1] Corman and Langlykke, *J. Bact.*, 1947, **54**, 149.

of maltose and dextrins (α-amylase-type action), in others there was rapid production of glucose. In 1953, Barker and Carrington [2] reported that a cell-free extract of *A. niger* "152," the strain responsible for the synthesis of nigeran, gave glucose as the major product of its action on starch. The purpose of the present communication is to describe the purification of this enzyme, termed glucamylase, which gives glucose as the sole product of its action on amylose. This enzyme appears to belong to a general group of enzymes, the glucamylases or amyloglucosidases, which probably include that isolated from *Clostridium acetobutylicum*,[3,4] and those reported in *Rhizopus delemar*,[5,6] *Aspergillus oryzae*,[7] *and A. niger* [8] (NRRL-330-1).

Purification of the glucamylase was followed by observing the changes in shape of the iodine-absorption value (A.V.)–reducing power curve obtained with each enzyme fraction after incorporation in a standard amylose digest devised so that neither the amylose nor the concentration of acetate buffer had any effect on the method of estimating the glucose produced. Such a curve is independent of the concentration of enzyme employed and characteristic of the type of enzyme(s) present.[9] With the crude cell-free extract of *A. niger*, the shape of the curve (see Figure) was reminiscent of the action of α-amylase



Enzyme fractions obtained during the purification of glucamylase.

A, Purified glucamylase; *B*, fraction 2 after treatment at pH 2·36; *C*, band A enzyme from crude extract; *D*, crude enzyme extract; *E*, enzyme in band B of crude extract.

on amylose, but was not reliable since the extract exhibited glucose oxidase and other activity towards glucose (Table 3). Glucose was, however, the only sugar detectable by paper chromatography throughout the incubation. As previously reported,[2] the crude extract also contains transglycosidases which act on sucrose and maltose. The crude enzyme extract could be stored for 1 month at 0° with only a small loss of amylolytic activity (Table 4) and was obtained with full activity in the freeze-dried form.

Addition of solid ammonium sulphate (20, 40, and 60 g.) to a solution of crude extract (100 c.c.) gave fractions 1, 2, and 3 respectively. Fraction 2 contained 85% of the activity recovered, and 40% of the original activity (Table 6). It was free from glucose oxidase (Table 6) and the transglucosidase which acts on maltose to give, *inter alia*, isomaltose and panose. The removal of glucose oxidase from the crude extract caused a shift in the absorption value–reducing power curve (Table 6), and again glucose was the only sugar detectable.

In order to determine whether this action was due to a single enzyme, fraction 2 and the crude enzyme extract were examined by paper chromatography with aqueous acetone as the irrigating solvent. To locate the amylolytic enzymes the chromatograms were

[2] Barker and Carrington, *J.*, 1953, 3588.
[3] Hockenhull and Herbert, *Biochem. J.*, 1945, **39**, 102.
[4] French and Knapp, *J. Biol. Chem.*, 1950, **187**, 463.
[5] Phillips and Caldwell, *J. Amer. Chem. Soc.*, 1951, **73**, 3559.
[6] Fukumoto, Sakazaka, and Minamii, *Symp. on Enz. Chem. (Japan)*, 1954, **9**, 94.
[7] Drews, Specht, and Olbrich, *Branntweinwirtschaft*, 1954, **76**, 21.
[8] Kerr, Cleveland, and Katzbeck, *J. Amer. Chem. Soc.*, 1951, **73**, 3916.
[9] Bourne, Macey, and Peat, *J.*, 1945, 882.

divided into narrow horizontal strips and, after incubation with a solution of amylose, the absorption value of each digest was determined. Amylolytic activity was located in two bands with both fraction 2 and the crude enzyme extract. The enzyme (R_F 0·036—0·143) of band A, eluted from a chromatogram of the crude extract, exhibited a marked change in the shape of the A.V.—reducing power curve (Figure). In addition, the wavelength of maximum absorption of iodine-stained aliquot portions of the digest did not shift to lower wavelengths throughout most of the time of incubation. This phenomenon was the opposite to that which had been observed with the crude extract, fraction 2, and α-amylase, and was typical of a β-amylase-type action except that, instead of maltose being progressively removed from the non-reducing ends of the amylose chains, the moiety removed was glucose. Attempts to elute the enzyme (R_F 0·475—0·571) from band B were unsuccessful and so the activity of this band was determined on paper. The results (Table 7) suggested that this band contained an α-amylase (random fission).

Purification of fraction 2 on a larger scale followed the example of other workers [5, 8] who freed glucamylase from α-amylase by treatment with acid. Treatment of fraction 2 at successively lower values of pH and determination of the nature of the residual activity showed a change, indicative of the removal of α-amylase, after treatment at pH 3·1 or below for 6 days (Table 8). The standard method adopted for the preparation of glucamylase was the treatment of fraction 2 at pH 2·9 for 12 days at 10°.

The shape of the A.V.–reducing power curve of this acid-treated enzyme (Figure) showed that it contained even less α-amylase than did the enzyme eluted from band A of the chromatogram of the crude extract. Moreover, chromatography of the acid-treated enzyme disclosed only one enzyme capable of hydrolysing amylose to products which were not stained by iodine; the R_F value of this enzyme was the same as that of band A.

The optimum pH and temperature of the acid-treated enzyme for its action on amylose were *ca.* pH 4·0 and 52° respectively. A minimum concentration (0·02M) of acetate buffer was necessary for the enzyme to exhibit its full activity. An attempt to find an alternative method of preparation by preferential inhibition of the α-amylase impurity in the crude extract was unsuccessful. Although mercuric chloride (50 parts per million) inhibited salivary α-amylase completely and had little effect on the acid-treated enzyme (Table 16), it did not inhibit appreciably the α-amylase in the crude extract (Table 5). The major portion of this mould α-amylase appears to be absorbed on the nigeran released during the disruption of the *A. niger* cells, since in the early stages of the action of a suspension of nigeran on amylose an appreciable concentration of maltose was formed, together with some maltotriose and higher oligosaccharides.

The action of glucamylase on amylose was not reversible (Table 14) and was not competitively inhibited by the product of its action, glucose (Table 15).

The glucamylase, purified by the procedures described, was thus seen to be substantially free from α-amylase, and also from other enzymes (including glucose oxidase and transglucosidase) capable of acting upon amylose or the possible products of the action of glucamylase on amylose.

Experimental

Standard Digest for the Measurement of Glucamylase Activity.—Amylose (80—100 mg.), moistened with ethanol, was dissolved in 0·2N-sodium hydroxide (10 c.c.) by warming at 60° for 2—3 min. After cooling, the solution was diluted to 25 c.c. and a portion containing 25 mg. of amylose (B.V. 1·24) was neutralised with 0·5N-sulphuric acid. This was incorporated in the standard digest (total volume, 25 c.c.) which also contained M-acetate buffer (2 c.c.) and glucamylase solution (5 c.c.). Before the isolation of the purified enzyme the digest was buffered at pH 6·0 and incubated at 37°; thereafter the buffer solution had pH 4·0, and the digest was incubated at 50° in a glass-stoppered flask. At intervals, aliquot portions (1 c.c.; equiv. to 1 mg. of amylose) were stained with iodine (2 mg.) and potassium iodide (20 mg.) in

a final volume of 100 c.c. and the A.V. 680 mμ measured.[10] Other portions (4 c.c.) were subjected to the Shaffer–Hartmann determination [11] of reducing sugar. Where the reducing power of the solution was suspected to be <0·5 mg., a solution (1 c.c.) containing a known amount of glucose was added before determination. Where reducing power (Red_G) is quoted it is expressed as a percentage of the theoretically possible amount of glucose liberated on complete hydrolysis. For the comparison of different enzyme preparations the activity is expressed as the Red_G after 4 hours' incubation under standard conditions.

(a) *Effect of amylose on the method of estimation.* The amounts of glucose (0·475 mg.; 0·950 mg.) estimated by the Shaffer–Hartmann method [11] in the absence of amylose were in good agreement with those (0·470 mg.; 0·945 mg.) determined in the presence of amylose of the concentration which would normally be present in a sample taken for the determination of glucamylase activity.

(b) *Effect of the concentration of acetate buffer on the method of estimation.* The reducing powers of glucose at two concentrations were determined in the presence of acetate buffer, pH 4·0, of the strengths given in Table 1.

TABLE 1. *Effect of varying concentrations of acetate buffer.*

Molarity of acetate buffer	0·0	0·002	0·02	0·2	0·5	0·0	0·002	0·02	0·2	0·5
Glucose determined (mg.)	0·58	0·59	0·60	0·59	0·45	1·21	1·20	1·19	1·20	0·54
Glucose taken	0·59 mg.					1·18 mg.				

Preparation of a Crude Aspergillus niger *Extract.*—Mycelia of *A. niger* (strain 152) were grown aerobically on a sterile solution containing sucrose (15%) and the mineral components of Currie's medium [12] and incubated at 30° for 6 days. The mycelia were removed from the growing cultures, any portions showing sporulation were discarded, and the remainder was washed in several changes of tap water, followed by three changes of distilled water. After shredding of the mycelium in an "Atomix" blender, with sufficient water to make a thick paste, the cells were disrupted with glass beads for 20 min. at 0° in a Mickle shaker or in a vibratory ball mill. The smashed cells were extracted twice with water, the combined extracts being centrifuged to remove cell debris. Microscopic examination of the extract, after staining with carbol-fuchsin, showed the absence of whole cells in each of twenty fields examined.

(a) *Action of the crude extract on amylose.* The crude extract (5 c.c.) was incorporated in a standard digest (25 c.c.) and aliquot portions were removed at intervals for determination of reducing power and A.V. The results are given in Table 2.

TABLE 2. *Action of the crude extract on amylose.*

Time (hr.)	0·013	0·13	1·33	5·25	10	22	46	60
A.V. (680 mμ)	1·120	1·114	1·042	0·798	0·552	0·215	0·033	0·014
Red_G	1·1	—	1·6	6·8	10·1	19·2	33·4	49·0

(b) *Action of the crude extract on glucose and maltose.* Portions (5 c.c.) of the crude extract were incorporated in standard digests in which the amylose was replaced by glucose (1·88 mg./c.c.) or maltose (1·60 mg./c.c.). Both digests contained the same amount of sodium sulphate as that present in the standard digest. The reducing power was determined at intervals (Table 3).

TABLE 3. *Action of the crude extract on glucose and maltose.*

(i) *Glucose*							
Time (hr.)	0	0·013	0·13	1·0	2·0	18·0	36·0
Reducing power	1·88	1·83	1·64	1·475	1·39	1·30	1·60
(ii) *Maltose*							
Time (hr.)	0·006	0·13	0·5	1·0	2·0	4·0	6·0	24·0
Reducing power as glucose (mg.)	0·69	0·72	0·87	1·26	1·29	1·07	1·10	0·99

(c) *Stability of the crude extract on storage.* The action of a fresh aqueous extract of *A. niger* cells on amylose was determined in a standard digest and then redetermined after being stored at 0° for 1 month (cf. Table 4).

[10] Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924.
[11] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.
[12] Currie, *ibid.*, 1917, **31**, 15.

TABLE 4. *Stability of the crude extract.*

	Fresh extract		Extract stored for 1 month	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·013	0·873	4·5	0·908	3·1
0·065	0·834	5·75	0·902	5·0
0·45	0·630	11·5	0·688	9·8
2·0	0·303	18·9	0·401	18·4

(d) *Effect of mercuric chloride on the crude extract.* Two standard amylose digests, into one of which mercuric chloride solution (2·5 c.c. containing 0·00125 mg. of this salt) was incorporated, were prepared and the activities of the crude extract determined (Table 5).

TABLE 5. *Effect of mercuric chloride on the crude extract.*

	Without $HgCl_2$		With $HgCl_2$	
Time (hr.)	A.V. (680 mμ)	% of theor. reducing power	A.V. (680 mμ)	% of theor. reducing power
0·05	1·04	5·0	1·02	5·2
0·5	0·58	9·9	0·57	10·1
1·25	0·13	16·2	0·25	17·1
4·0	0·03	29·2	0·06	32·4
22·0	0·02	51·3	0·02	52·2

(e) *Removal of glucose oxidase activity by ammonium sulphate fractionation.* The activity of a portion (5 c.c.) of a crude extract (50 c.c.) was determined and solid ammonium sulphate (9·5 g., equiv. to 20 g. per 100 c.c. of solution) added to the remainder. After being kept overnight at 0°, the precipitate (fraction 1), which formed a solid cake on the surface after centrifugation, was separated and redissolved in water (45 c.c.). The concentration of ammonium sulphate was increased to 40 g./100 c.c. and 60 g./100 c.c. of the original solution, giving precipitates (fractions 2 and 3 respectively) which were each redissolved in water (45 c.c.). The activities of each fraction were determined with respect to amylose and in the case of fraction 2 with respect to glucose also.

TABLE 6. *Fractionation of the crude extract with ammonium sulphate.*

	Crude extract		Fraction 1		Fraction 2		Fraction 3	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·013	1·15	—	1·17	—	1·21	—	1·19	—
0·25	0·85	1·2	1·14	0·2	1·20	0·2	1·17	0·2
1·0	0·60	6·5	1·10	1·1	1·10	1·9	1·16	0·2
2·5	0·31	11·7	1·05	1·5	0·68	3·25	1·16	0·7
21·0	0·02	65·6	0·93	3·4	0·28	25·8	1·07	1·1

Action of fraction 2 on glucose.

Time (hr.)	0·013	0·5	1·0	2·0	18·0	114·0
Reducing power as glucose (mg.)	1·88	1·87	1·875	1·875	1·85	1·83
Glucose destroyed (% of theory)	0·0	0·53	0·26	0·26	1·60	2·66

Separation of Enzymic Components by Paper Chromatography.—(i) *Crude* A. niger *extract-activities of bands A and B.* Freeze-dried crude enzyme extract (100 mg.) was dissolved in water (0·4 c.c.) and placed, in two applications, along lines (20 cm. long) drawn on two strips of filter paper (23 cm. wide). After irrigation with 50% aqueous acetone for 7 hr. at 0°, the paper was dried in a current of cold air. Strips (3 cm. wide) were cut from each side of the chromatogram and the position of those enzymes exhibiting amylolytic activity determined by examination of portions (1 cm. long) of these strips. Each small strip was incubated with 0·05% amylose solution (1 c.c.), and 0·02M-phosphate (pH 6·18)–0·03M-sodium chloride buffer (5 c.c.) for 6 hr. at 37°. Aliquot portions (5 c.c.) of each digest were withdrawn, acidified with N-sulphuric acid (1 c.c.), and stained with 0·006% iodine solution (1 c.c.). The location of the enzyme was indicated by a decrease in the absorption value (680 mμ) measured in 1 cm. cells. Amylolytic activity was exhibited by two distinct bands on the chromatogram. Band A enzyme, which had R_F 0·036—0·143, could be completely eluted from the paper (4 cm. wide) with 6 c.c.

of 0·02M-phosphate buffer (pH 6·18). Band B enzyme, which had R_F 0·465—0·571, was not extracted from the paper under the same conditions and its activity was therefore determined with the enzyme still intact on the paper. The activities of both Band A and B enzymes, after incorporation in standard digests, are given in Table 7.

TABLE 7. *Activities of amylolytic enzymes in bands A and B.*

Enzyme in band A							
Time (hr.)	0·083	6·0	22·0	46·0	94·0		
A.V. (680 mμ)	1·13	0·82	0·58	0·31	0·03		
Red_G	0·7	6·7	15·0	26·8	47·3		
Enzyme in band B							
Time (hr.)	0·083	1·0	6·0	24·0	48·0	96·0	144·0
A.V. (680 mμ)	1·13	1·06	0·83	0·54	0·47	0·25	0·16
Red_G	0·45	0·9	1·6	2·7	3·8	6·3	13·3

(ii) *Ammonium sulphate-purified enzyme.* Fraction 2 was separated on filter paper as described above for the crude enzyme, and the amylolytic enzymes were located. The amylolytic activity was again located in two distinct bands, A (R_F 0·040—0·12) and B (R_F 0·40—0·52).

Purification of Fraction 2 by Acid-treatment.—(i) *Effect of storage at different* pH *values.* Portions (5 c.c.) of the enzyme preparation described as fraction 2 were adjusted to various pH values (Table 8) with N-sulphuric acid and stored at 0° for 6 days. Each solution was then adjusted to pH 6·0 with N-sodium hydroxide, and its activity determined by using standard amylose digests. A further portion (5 c.c.) of fraction 2 (pH 5·22), to which no acid was added, was similarly treated and served as a control.

TABLE 8. *Acid treatment of fraction 2.*

	pH 5·22		pH 3·98		pH 3·12		pH 2·36	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·067	1·07	—	1·09	—	1·08	—	1·09	—
0·5	0·74	3·4	0·82	2·6	0·99	2·25	0·96	3·6
1·5	0·59	4·8	0·66	4·0	0·91	3·7	0·83	4·7
5·0	0·32	10·0	0·38	9·5	0·74	11·0	0·75	9·4
24·0	0·08	31·8	0·14	27·0	0·16	36·0	0·22	36·0
52·0	0·01	61·6	0·02	52·8	0·08	53·2	0·10	50·4

(ii) *Chromatography of acid-treated enzyme.*—A solution of glucamylase, obtained by treatment of fraction 2 at pH 2·0 and 10° for 12 days, was examined by paper chromatography as described for the crude extract. Only one band was now observed which had amylolytic activity and this had an R_F value (0·038—0·19) similar to that of band A. All glucamylase used below had been subjected to this acid-treatment.

Optimum pH *Value for Glucamylase Action.*—A number of standard amylose digests were prepared, incorporating M-acetate buffer (2 c.c.) of different pH values from 2·94 to 6·96. The activity of acid-treated glucamylase in each digest was determined in the usual way (see Table 9).

TABLE 9. *Activity of glucamylase at different* pH *values.*

	pH 2·94		pH 4·00		pH 5·00		pH 5·98		pH 6·96	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·026	1·09	0·7	1·08	0·4	1·09	0·9	1·10	0·9	1·09	0·7
1·0	0·95	8·3	0·86	10·8	0·85	11·0	0·95	5·6	1·06	3·8
4·0	0·44	21·6	0·28	32·2	0·29	34·2	0·65	17·1	0·99	7·0
24·0	0·02	63·0	0·02	70·1	0·02	54·9	0·03	47·7	0·64	20·2

Optimum Temperature of Glucamylase Action.—Glucamylase solution was incorporated into each of five standard amylose digests buffered at the optimum pH value (4·0). These digests were incubated at different temperatures between 37° and 70°. The results of activity determinations are given in Table 10.

TABLE 10. *Activity of glucamylase at different temperatures.*

	37°		44°		50°		60°		70°	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·026	1·13	2·2	1·11	2·5	1·11	2·5	1·12	2·5	1·14	2·5
1·0	0·71	14·6	0·67	18·9	0·47	24·5	0·65	19·1	0·89	5·9
4·0	0·34	32·8	0·29	31·6	0·03	43·8	0·18	37·4	0·86	6·3
24·0	0·01	62·6	0·01	67·5	0·01	83·6	0·01	59·0	0·86	6·1

Influence of Ionic Concentration on the Activity of Glucamylase.—A series of standard amylose digests was prepared incorporating acetate buffer (pH 4·0; 5 c.c.) of varying molarity so that the concentration of each digest with respect to acetate buffer was that given in Table 11. The effect on the activity of glucamylase was determined.

TABLE 11. *Influence of ionic concentration on activity.*

	0·2M		0·02M		0·002M		Nil	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·067	1·14	0·9	1·14	0·4	1·15	0	1·15	0·9
1·0	0·89	9·2	0·80	13·5	1·05	5·4	1·10	4·0
4·0	0·38	28·8	0·32	32·9	0·80	11·7	0·90	7·4
22·0	0·01	67·6	0·01	71·1	0·01	50·0	0·09	44·1

Stability of Glucamylase to Acid.—Portions (5 c.c.) of glucamylase were acidified with sulphuric acid to pH 2·04, 1·50, 1·02, and 0·44 respectively. After 12 days at 10° they were neutralised to pH 6·0 ± 0·1 with sodium hydroxide, and the activity of each determined in a standard amylose digest (cf. Table 12).

TABLE 12. *Stability of glucamylase to acid.*

	pH 2·04		pH 1·50		pH 1·02		pH 0·44	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·067	1·11	0·4	1·09	0·9	1·12	0·9	1·12	0·9
3·0	0·76	8·1	1·09	0·7	1·11	0·9	1·11	0·7
22·0	0·06	46·8	1·10	0·4	1·13	0·7	1·12	0·4
48·0	0·01	54·8	1·06	0·3	1·07	0·4	1·05	0·3

Action of Glucamylase on Amylose.—The amylose was dried over phosphoric oxide for 16 hr. at 60°/0·002 mm. A sample was hydrolysed in 2N-sulphuric acid for 5 hr. and the reducing power determined. After a correction for the loss of glucose during hydrolysis the purity of the amylose was calculated to be 96·5%. This amylose was incorporated into a standard digest and the activity of the glucamylase determined in the usual way (see Table 13).

TABLE 13. *Action of glucamylase on amylose.*

Time (hr.)	0·026	1·0	4·0	24·0	48·0	192·0
A.V. (680 mμ)	1·33	1·01	0·45	0·02	0·01	0·01
Red_G	0	12·5	44·2	91·8	93·2	98·0

Paper-chromatographic examination of a similar digest revealed only one component, with an R_F value equal to that of glucose. This was the only sugar which could be detected throughout the action of glucamylase on amylose.

Stability of Glucose to Glucamylase Action.—A digest was prepared containing glucose (17 mg.),

M-acetate buffer (pH 4·0; 2 c.c.), and glucamylase solution (5 c.c.) in a total volume of 25 c.c. The digest was incubated at 50° and aliquot portions (2 c.c.) were withdrawn at intervals for the determination of reducing power. When these were analysed paper-chromatographically, no sugar other than glucose was detected in the digest (Table 14).

TABLE 14. *Action of glucamylase on glucose.*

Time (hr.)	0·067	0·5	2·5	18·0	42·0	66·0	138·0	210·0
Reducing power as glucose (mg.)	1·35	1·35	1·36	1·35	1·36	1·36	1·35	1·34

Amylolysis in the Presence of Glucose.—Three standard digests were prepared, and glucose (10 mg.; 25 mg.) incorporated in two of them. The action of glucamylase was then determined under these conditions (see Table 15).

TABLE 15. *Amylolysis in the presence of glucose.*

	No added glucose		Glucose (10 mg.)		Glucose (25 mg.)	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·013	1·08	2·7	1·10	3·1	1·12	3·6
1·0	0·28	37·8	0·25	41·4	0·24	39·6
3·0	0·01	94·5	0·01	96·4	0·01	94·5
25·0	0·01	99·0	0·01	98·1	0·01	98·4

Action of Mercuric Chloride on Glucamylase and α-Amylase.—Saliva (4 c.c.) was diluted with water (6 c.c.) and the mucin removed by centrifuging the mixture. The supernatant liquid was diluted to 150 c.c. The activities of the salivary α-amylase and glucamylase were determined at pH 5·0 and 37° in standard digests in the presence and absence of mercuric chloride (0·00125 mg.). Results are in Table 16.

TABLE 16. *Effect of mercuric chloride on glucamylase and α-amylase.*

	Salivary α-amylase			Glucamylase	
Time (hr.)	Without $HgCl_2$ Red_G	With $HgCl_2$ Red_G	Time (hr.)	Without $HgCl_2$ Red_G	With $HgCl_2$ Red_G
0·067	4·2	0·2	0·067	1·6	1·6
1·0	5·9	0·0	1·0	17·5	17·5
3·5	7·2	0·0	4·0	57·8	54·4
21·0	10·8	0·2	20·0	62·9	64·8
45·0	19·8	0·2			

Amylase Adsorbed on the Intracellar Nigeran.—The rupture of *A. niger* cells, for the extraction of glucamylase, releases the nigeran which, on centrifugation, is obtained as a layer on top of the cell debris. This nigeran (600 mg.) was suspended in water (15 c.c.), and a portion (2 c.c.) incorporated in a digest containing amylose (50 mg.) [in 0·08N-sodium sulphate solution (2·5 c.c.)] and M-acetate buffer (pH 4·0; 0·5 c.c.) which was incubated at 37°. Aliquot portions (30 μl.) were withdrawn at intervals and examined by paper chromatography.

The same suspension (diluted 5 times; 5 c.c.) of nigeran was incorporated in a standard amylose digest and its activity determined (Table 17) at 37°.

TABLE 17. *Action on amylase.*

Time (hr.)	0·33	1·5	2·5	4·0	8·5	12·0	24·0
A.V. (680 mμ)	1·11	1·01	0·66	0·39	0·18	0·12	0·04
% of theor. reducing power as glucose	1·0	3·3	4·3	8·25	19·6	27·0	52·9

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978. *Studies on* Aspergillus Niger. *Part IX.*[1] *The Mechanism of Glucamylase Action.*

By S. A. Barker, E. J. Bourne, and J. G. Fleetwood.

The action of glucamylase, prepared by the standard method.[1] on some thirty oligo- and poly-saccharides is reported. It is shown that the attack of glucamylase on various amylosaccharides is multi-chain and consists of the stepwise removal of single glucose units from the non-reducing ends of the chains.

After the isolation [1] of a purified glucamylase from the strain of *Aspergillus niger* responsible for the synthesis of nigeran [2] the specificity and mechanism of its action were investigated. As a preliminary step, amylosaccharides (maltotriose, maltotetraose, maltopentaose, and maltohexaose) were isolated in a chromatographically pure state by fractionation of the partial acid hydrolysis products of amylose on a charcoal column.[3,4] The purity of each (95—98%) was determined by estimation of the glucose produced by complete acidic hydrolysis.

Maltose, maltotriose, maltotetraose, and maltopentaose were each converted quantitatively into glucose by glucamylase (Table 3). Paper chromatography showed that the main attack of the glucamylase was by end-wise removal of single glucose units. Thus, during the initial attack of the glucamylase on maltotetraose and maltopentaose, only the next lower member of the homologous series and glucose could be detected. The relative concentrations of the various amylosaccharides produced during the reactions suggested that the mechanism was primarily a multi-chain and not a single-chain attack.

Evidence that the glucamylase attacked the non-reducing end of oligosaccharides was obtained by studying the action of the enzyme on the isomeric trisaccharides produced by partial acid hydrolysis of nigeran. While *O*-α-D-glucopyranosyl-(1 → 3)-*O*-α-D-glucopyranosyl-(1 → 4)-D-glucopyranose (T1) was immune to glucamylase, *O*-α-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 3)-D-glucopyranose (T2) gave nigerose and glucose. Again, calcium maltobionate was rapidly attacked, to give calcium gluconate and glucose. Further evidence in favour of an endwise attack by glucamylase was its inability to hydrolyse Schardinger cyclic dextrins (Table 4).

Table 1. *The specificity of glucamylase.*

Substrates not attacked: Glucose, methyl α-D-glucopyranoside, methyl β-D-glucopyranoside, dipotassium α-D-glucose 1-phosphate, αα-trehalose, nigerose, trisaccharide T1, isomaltose, dextran, α- and β-Schardinger dextrins, laminaribiose, gentiobiose, cellobiose, turanose, melibiose, lactose, *O*-α-D-mannopyranosyl-(1 → 6)-D-mannose, melezitose, maltulose.

Substrates attacked only very slowly: Sucrose, raffinose, isomaltotetraose, panose.

Substrates rapidly and completely hydrolysed: Maltose, maltotriose, maltotetraose, maltopentaose amylose, calcium maltobionate, trisaccharide T2.

Table 1 shows that of 29 linear substrates examined, in general only those containing a terminal α-glucopyranosyl residue linked to position 4 of a second glucopyranose unit were attacked at an appreciable rate. Clearly the two glucose units are concerned jointly in providing suitable sites for the enzyme. It is of interest, for example, that maltulose is not a substrate, whereas calcium maltobionate (the only exception to the generalisation) is a good one, presumably because the latter can adopt a shape in which the acyclic moiety approximates sufficiently closely to a second glucose unit to form a template for the enzyme. Panose and isomaltotetraose were degraded very slowly by the enzyme; the former gave glucose and maltose as the initial products, probably as a result of a slight enzymic

[1] Part VIII, Barker and Fleetwood, preceding paper.
[2] Barker, Bourne, and Stacey, *J.*, 1953, 3084.
[3] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[4] Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826.

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impurity. Likewise the enzyme had a very slow action on sucrose; minute amounts of glucose and fructose could be detected in the digest after 48 hr. A similar rate of hydrolysis was observed with raffinose.

Although the glucamylase preparation resembles β-amylase in its attack on the non-reducing end of the chain, it differs in its action on sodium starch glycollate. β-Amylase cannot hydrolyse the glycollate beyond the first substituted glucose residue and with this substrate showed only a very slow action up to 8·8% hydrolysis. Glucamylase produced considerably more reducing sugar than this and achieved a 35% conversion of sodium starch glycollate in 24 hr. (Table 6). Since this apparent ability of the glucamylase to hydrolyse α-1 : 4-glucosidic linkages beyond the substituted residues could be explained by the presence of a very small amount of α-amylase, the action of glucamylase on amylose was examined more closely in order to determine the proportion of this random attack.

A glucamylase-type enzyme could hydrolyse amylose molecules by random attack or by end-wise action; in the latter case it could be either a single-chain action (degradation of one chain at a time) or a multi-chain action (degradation of all chains simultaneously). The relation between the degree of polymerisation (D.P.) of the residual amylose and the degree of hydrolysis (measured as glucose) would be different in the various cases. The intrinsic viscosity $[\eta]$ of solutions of many polymers has been shown to be related to the average molecular weight $\overline{M}$ by the expression $[\eta] = K\overline{M}^a$ which was derived empirically by Flory.[5] Amylose (intrinsic viscosity 1·7) of D.P. about 2000, prepared under anærobic conditions,[6] was incorporated into a digest containing acetate buffer and glucamylase and incubated. Portions of this digest were withdrawn at intervals for the determination of A.V., reducing power, and intrinsic viscosity, measured in 0·5N-sodium hydroxide. A control digest, containing amylose and acetate buffer, but not glucamylase, was incubated alongside this digest so that the amount of degradation due to the acidity of the digest could be ascertained.

Table 7 shows that after 28% of the total number of bonds had been broken the intrinsic viscosity of the residual amylose was reduced to 33% of its original value. If a is taken as unity (the experimentally derived values of a for amylose and for cellulose esters vary between 0·83 and 1·05), then at this stage the intrinsic viscosity should have been 0·18, 72, and 100% of the original value, respectively, for random, multi-chain end-wise, and single-chain end-wise attack. Clearly a completely random attack was excluded. The discrepancy between the other two theoretical figures and the figure actually obtained may be attributed to a very small proportion of random fission (*e.g.*, by a trace of α-amylase). It would only be necessary to break by random attack 1—2 bonds per molecule in order to account for the discrepancy; for an initial D.P. of 2000 the number of bonds broken per molecule by end-wise attack at 28% conversion would be 560, and therefore only one random fission in 280—560 would cause the observed discrepancy. These conclusions are in agreement with absorption value–reducing power curves (see Part VIII).

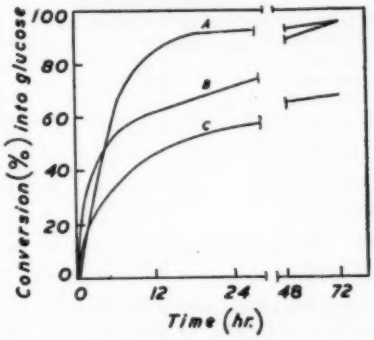
Unfortunately, even such a small amount of α-amylase activity is sufficient to make it impossible to distinguish between single-chain and multi-chain mechanisms on large molecules. The only direct evidence on this question, the chromatographic detection of a considerable amount of the next lower oligosaccharide when glucamylase is allowed to act on maltotetraose or maltopentaose, indicates a multi-chain mechanism. On the question of random or endwise attack, however, there seems little doubt that glucamylase acts by end-wise fission.

Amylopectin, limit β-dextrin (produced by the action of β-amylase on amylopectin), and amylose were compared with respect to both their rates of hydrolysis (see Figure) and their degree of susceptibility to glucamylase (Table 8). The Figure shows that, although the initial rate of hydrolysis of amylopectin was greater than that of amylose (in agreement with an end-wise attack), the rate of hydrolysis of amylopectin decreased sharply at about

[5] Flory, *J. Amer. Chem. Soc.*, 1943, **65**, 372.
[6] Baum and Gilbert, *Chem. and Ind.*, 1954, 490.

60% conversion, showing that the presence of 1 : 6-links hinders the normal action of glucamylase. The removal, by end-wise attack, of 60% of the total number of glucose residues would leave a molecule of the limit-dextrin type, and in agreement with this it is seen that the rate of hydrolysis of limit β-dextrin was similar to the rate of hydrolysis during the latter part of the hydrolysis of amylopectin. When the action of glucamylase on amylopectin, limit β-dextrin, or glycogen was followed on a paper chromatogram, isomaltose was detected in each case. Clearly these branched molecules were hydrolysed virtually completely after prolonged incubation, presumably because the inner chains were made accessible by the small amount of α-amylase impurity.

Additional evidence in favour of this conclusion was provided by the action on limit β-dextrin of glucamylase, which had been purified further on a chromatogram with an



The action of glucamylase on (A) amylose, (B) amylopectin, and (C) dextrin A.

aqueous-acetone solvent. The chromatogram was divided lengthwise into two parts; on one of these halves the position of the glucamylase was determined by its action on amylose; the other half of the chromatogram, when incubated with limit β-dextrin, caused no degradation of limit β-dextrin, either in the region which had been shown to contain glucamylase or in any other part of the chromatogram. It was shown that neither the paper, nor treatment with aqueous acetone, caused any loss in the activity of glucamylase on amylose or on limit β-dextrin. The failure of the chromatographed glucamylase to hydrolyse β-dextrin must therefore be due to the removal of an enzyme which either hydrolyses or by-passes the 1 : 6-links. Since it is known [1] that glucamylase and α-amylase are produced together by *A. niger* and that α-amylase has a greater mobility on paper in aqueous acetone, the most likely explanation is that the last trace of α-amylase in the glucamylase solution had been removed by chromatography.

Experimental

Preparation of Amylosaccharides.—Amylose (23 g.) was partially hydrolysed with 0·5N-sulphuric acid (2 l.) at 100° for 140 min. The reducing power of the hydrolysate then corresponded to a 34·2% conversion into glucose. After neutralisation with 5N-sodium hydroxide and removal of insoluble material (0·7 g.), the solution was concentrated *in vacuo* to 200 c.c., filtered, and dialysed against distilled water for 3 hr., the water being changed every hour. The saccharide mixture remaining in the dialysis tube was fractionated on a charcoal column (65 × 5·5 cm.), which was washed by gradient elution [4] with water containing increasing concentrations of ethanol. The eluates were filtered, concentrated, freeze-dried, and then analysed by paper chromatography.

The purity of each major fraction, measured by determination of the glucose formed after hydrolysis in 2N-sulphuric acid at 100° for 4 hr., was: maltotriose, 96%; maltotetraose, 95%; maltopentaose, 98%; maltohexaose, 95%.

Action of Glucamylase on Amylosaccharides.—A series of digests were prepared containing substrate (25 mg.), M-acetate buffer (pH 4·0; 2 c.c.), and glucamylase solution (5 c.c.) in a

total volume of 25 c.c. Each digest, in a glass-stoppered flask, was incubated at 50°, and aliquot parts (2 or 1 c.c.) were withdrawn at intervals for determination of reducing power.[7]

More concentrated digests were prepared containing substrate (25 mg.) dissolved in water (0·25 c.c.), M-acetate buffer (pH 4·0; 0·04 c.c.), and glucamylase solution (0·2 c.c.) and analysed by paper chromatography with the organic phase of a butan-1-ol–ethanol–water–ammonia mixture (40 : 10 : 49 : 1). The oligosaccharides were detected by spraying with aniline hydrogen phthalate.[8] Maltose gave progressively increasing amounts of glucose and was no longer detectable after 72 hr. In the initial stages (up to 8 hr.), maltotriose gave roughly equimolar quantities of maltose and glucose but thereafter the former rapidly disappeared. The maltotriose was completely converted into glucose after 72 hr. Maltotetraose gave maltotriose and

TABLE 2. *Isolation of amylosaccharides.*

Concn. (%) of EtOH in eluant	Rate of change of EtOH concn. (% per l.)	Sugar component	Yield (g.)	$[\alpha]_D^{17}$ in H_2O
10—15	2·5	Maltose	Trace	—
15—18	1·5	—	—	—
18—21·5	1	Maltotriose	1·865	+157°
21·5—23	1	Maltotriose + Maltotetraose	Trace	—
23—24·2	1	Maltotetraose	1·254	+169
24·2—25·2	1	Maltotetraose + Maltopentaose	1·192	—
25·2—26·2	0·5	Maltopentaose	0·350	+182
26·2—26·8	0·5	Maltopentaose + Maltohexaose	0·460	—
26·8—34	0·5	Maltohexaose	0·269	+177

glucose during the initial stages (up to 8 hr.) and no maltose was detectable. Thereafter the maltotriose was attacked to give maltose, and eventually all the amylosaccharides were hydrolysed enzymically to glucose. The initial products of the action of glucamylase on maltopentaose were maltotetraose and glucose. Thereafter the course of the reaction followed that just described with maltotetraose.

Action of Glucamylase on the Isomeric Trisaccharides from Nigeran.—A mixture containing

TABLE 3. *Action of glucamylase on amylosaccharides.*

Time (hr.)	Conversion (%) into glucose of: Maltose	Maltotriose	Maltotetraose	Maltopentaose
1	19·0	62·5	83·8	74·4
3	81·1	100·0	97·5	96·6
5	82·1	100·4	98·8	100·1
23	94·3	100·6	100·0	100·1
47	98·3	100·6	100·2	100·4

two trisaccharides (50 mg.), namely, *O*-α-D-glucopyranosyl-(1 ⟶ 4)-*O*-α-D-glucopyranosyl-(1 ⟶ 3)-D-glucopyranose (T2) and *O*-α-D-glucopyranosyl-(1 ⟶ 3)-*O*-α-D-glucopyranosyl-(1 ⟶ 4)-D-glucopyranose (T1), in water (0·6 c.c.) was incubated with M-acetate buffer (pH 4·0; 0·1 c.c.) and glucamylase (0·3 c.c.), and the progress of the reaction was followed by paper ionophoresis in borate buffer [9] (pH 10·0). Glucose and nigerose were progressively liberated from trisaccharide T2 which could not be detected after 17 hr. Trisaccharide T1 was not

TABLE 4. *Action of glucamylase on the Schardinger dextrins.*

Time (hr.)	0·067	1·5	4·0	22·0	48·0	72·0
Conversion (%) into glucose: α-dextrin	1·6	1·6	2·2	1·8	2·2	2·0
Conversion (%) into glucose: β-dextrin	3·1	2·5	3·1	2·5	2·7	3·1

attacked even after 92 hr. The M_G values of the possible components were T2, 0·62; T1, 0·32; maltose, 0·34; nigerose, 0·73.

Action of Glucamylase on Schardinger Dextrins.—Schardinger α(or β)-dextrin (25 mg.), after

[7] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.
[8] Partridge, *Nature*, 1949, **164**, 443.
[9] Foster, *J.*, 1953, 982.

being dissolved in 0·2N-sodium hydroxide (5 c.c.) and neutralised, was incorporated in a digest (total volume, 25 c.c.) which also contained M-acetate buffer (pH 4·0; 2 c.c.) and glucamylase (5 c.c.). The reducing power was measured at intervals (see Table 4). Chromatography of more concentrated digests failed to reveal any reducing sugar during an incubation period of 150 hr.

Action of Glucamylase on Various Substrates.—The action of glucamylase on a wide range of substrates (Table 1) was examined by paper chromatography. For this purpose digests, containing the substrate (50 mg.) in water (0·5 c.c.), M-acetate buffer (pH 4·0; 0·1 c.c.), and glucamylase solution (0·4 c.c.) were incubated at 50°, and aliquot portions (10 µl.) withdrawn at intervals for paper chromatography.

To see whether the glucamylase exhibited phosphatase activity, the enzyme (5 c.c.) was incorporated in a digest (total volume, 25 c.c.) containing dipotassium α-D-glucose 1-phosphate (50 mg.) and M-acetate buffer (pH 5·96; 2 c.c.). A similar digest, to which a 1% solution (0·1 c.c.) of soluble starch was added, was used for the detection of any phosphorylase activity. Both digests were incubated at 37° and aliquot portions (2 c.c.) withdrawn for the determination of inorganic phosphate [10] (see Table 5).

TABLE 5. *Action of glucamylase on glucose* 1*-phosphate.*

Time (hr.)		0·013	1·0	3·0	5·0	24	30
Hydrolysis (%) of G 1-P	no starch	2·4	2·7	2·7	3·0	—	3·9
	starch added	2·7	2·7	3·0	3·0	3·9	—

TABLE 6. *Action of amylases on sodium starch glycollate.*

	α-Amylase		β-Amylase		Glucamylase	
Time (hr.)	A.V. (680 mµ)	Apparent conversion (%) into glucose	A.V. (680 mµ)	Apparent conversion (%) into glucose	A.V. (680 mµ)	Apparent conversion (%) into glucose
0·033	0·074	6·9	0·285	4·1	0·279	4·1
2·0	0·011	33·8	0·254	7·4	0·195	14·5
24·0	0·010	40·2	0·168	8·8	0·032	35·6
48·0	0·010	43·0	0·132	9·0	0·014	44·8
72·0	0·012	44·9	0·125	8·8	0·011	48·1

Action of Glucamylase on Sodium Starch Glycollate.—Three digests (each 25 c.c.) were prepared containing sodium starch glycollate (95·5 mg.) and M-acetate buffer (2 c.c.) with glucamylase, salivary α-amylase, or soya-bean β-amylase. The digests containing α- and β-amylase were buffered at pH 5·0 and incubated at 28°, while that containing glucamylase was buffered at pH 4·0 and incubated at 50°. The reducing power and A.V. 680 mµ [11] were measured at intervals (see Table 6).

Relation Between the Intrinsic Viscosity and Degree of Hydrolysis of Amylose by Glucamylase.—Amylose (B.V. 1·12) was isolated under anærobic conditions by Baum and Gilbert's method.[6] The amylose (21·9 mg.) was dissolved in cold 0·5N-sodium hydroxide (12 c.c.) and filtered, through a grade-4 sintered-glass filter, into a carefully cleaned, and dried, dust- and fibre-free vessel. This solution (10 c.c.) was transferred to a modified Ubbelohde viscometer (flow time for 0·5N-sodium hydroxide at 20°, 179·2 sec.) and the viscosity measured; the utmost care was exercised during the measurements to prevent the entry of dust or fibres into the viscometer. The solution was diluted to $\frac{2}{3}$, $\frac{1}{2}$, and $\frac{1}{3}$ of the original concentration with 0·5N-sodium hydroxide, and the specific viscosity was determined at each concentration; the mean value of at least four flow-time measurements, which did not differ by more than 0·4 sec. from each other, was taken for the calculation. The intrinsic viscosity was obtained by extrapolating the value of η_{sp}/c to zero concentration (Table 7).

Amylose (120 mg.) was dissolved in cold 0·5N-sodium hydroxide (20 c.c.), and the solution neutralised with sulphuric acid; M-acetate buffer (pH 4·0; 2 c.c.) and glucamylase (2 c.c.) were added and the digest was diluted to 40 c.c. with water and incubated at 50°. Samples (10 c.c.) were withdrawn at intervals, inactivated with 6% trichloroacetic acid (1 c.c.), then centrifuged, and the supernatant solutions neutralised. 7·5N-Sodium hydroxide (2 c.c.) was added to the

[10] Allen, *Biochem. J.*, 1940, **34**, 858.
[11] Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924.

supernatant solution which was then diluted to 15 c.c. with water. Part (10 c.c.) of this solution was used for the determination of the intrinsic viscosity of the residual amylose. Simultaneously with the withdrawal of the samples for the viscosity determinations, aliquot portions (0·33 and 1 c.c.) were withdrawn for the determination of A.V. and reducing power respectively.

TABLE 7. *Relation between the intrinsic viscosity and the degree of hydrolysis.*

Original amylose:				
Concn. (%)	0·182	0·122	0·091	0·061
η_{sp}/c	2·14	1·98	1·93	1·83
Amylose from control digest:				
Concn. (%)	0·200	0·133	0·100	0·067
η_{sp}/c	2·16	1·97	1·84	1·72
11·4% Hydrolysed amylose:				
Concn. (%):	0·177	0·118	0·089	0·059
η_{sp}/c	1·23	1·09	1·02	0·95
27·9% Hydrolysed amylose:				
Concn. (%)	0·144	0·096	0·072	0·048
η_{sp}/c	0·98	0·83	0·71	0·65

Time (hr.)	A.V. (680 mμ)	% of theor. reducing power	Intrinsic viscosity
0	0·97	—	1·70
0·017	0·94	0·6	—
0·167	0·82	11·4	0·80
0·67	0·40	27·9	0·52
1·33	0·03	78·0	—
			1·56 (control)

A control digest, similar to the above digest but without glucamylase, was prepared and incubated, inactivated, etc., as above, and the intrinsic viscosity determined.

Action of Glucamylase on Amylopectin and on Limit β-Dextrin.—The substrate (25 mg.) was dissolved in 0·2N-sodium hydroxide (5 c.c.) and neutralised with sulphuric acid. M-Acetate buffer (pH 4·0; 2 c.c.) and glucamylase (5 c.c.) were added and the digest was diluted, with water, to 25 c.c. The absorption value and reducing power were measured at intervals (see Table 8).

TABLE 8. *Action of glucamylase on amylopectin and limit β-dextrin.*

	Amylopectin		Limit β-dextrin	
Time (hr.)	A.V. (680 mμ)	Red_G	A.V. (680 mμ)	Red_G
0·033	0·183	0·6	0·142	0
1·0	0·120	28·7	0·114	16·0
4·0	0·054	44·6	0·051	28·1
24·0	0·013	71·2	0·017	55·8
48·0	0·011	89·2	0·013	65·7
72·0	0·012	95·7	0·011	68·4
192·0	0·010	96·7	0·011	74·7

Paper chromatography of more concentrated digests containing amylopectin and limit β-dextrin showed that the main reducing sugar produced was glucose. In addition, another reducing sugar was detected which had an R_F value identical with that of isomaltose in two different solvent systems. Its M_G value in borate buffer (pH 10·0) was identical.

Action of Chromatographically Purified Glucamylase on Limit β-Dextrin.—Glucamylase (0·2 c.c.) was applied to a strip of Whatman No. 1 filter paper, irrigated with 50% aqueous acetone at 0° for 7 hr., dried in cold air, and divided into 1 cm. strips. The position of the glucamylase was determined by estimating the reducing power produced after incubating half of each strip with a solution of amylose (1 mg.) for 24 hr. The other half of each strip was incubated with dextrin A (1 mg.) for the same time and the reducing power of each digest determined. Determinations were carried out in the presence of 0·12 mg. of glucose (see Table 9).

TABLE 9. *Action of chromatographically purified glucamylase on limit β-dextrin.*

Strip no:	1	2	3	4	5	6	7	8	9	10	11	12
	Reducing power as glucose (mg.)											
Amylose	0·15	0·12	0·25	0·38	0·35	0·25	0·12	0·12	0·10	0·08	0·10	0·10
Limit β-dextrin ...	0·14	0·14	0·12	0·15	0·12	0·12	0·10	0·10	0·12	0·08	0·12	0·10

Glucamylase solution (180 μl.) was applied to two strips of filter paper, which were put into two digests containing amylose (1 mg.) and limit β-dextrin (1 mg.) respectively. Two other similar digests were prepared containing glucamylase (180 μl.) but no filter paper. The four digests were incubated for 24 hr., after which the reducing power of each was determined:

Digest containing:	amylose + paper	amylose alone	limit β-dextrin + paper	limit β-dextrin alone
Reducing power as glucose (mg.) ...	0·63	0·65	0·26	0·25

A similar amount of glucamylase solution was applied to each of four strips of filter paper. Two of these strips were moistened with 50% aqueous acetone and kept in an atmosphere of the same solvent mixture for 4 hr. at 0°. These strips were allowed to dry in cold air and added to two digests containing amylose (1 mg.) and limit β-dextrin (1 mg.) respectively. The two other paper strips, not treated with acetone, were added to two similar digests, the four digests were incubated for 24 hr. and the reducing powers determined.

Digest containing:	acetone-treated enzyme + amylose	untreated enzyme + amylose	acetone-treated enzyme + β-dextrin	untreated enzyme + β-dextrin
Reducing power as glucose (mg.)	0·73	0·72	0·29	0·29

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979. *The Synthesis of Disaccharides.*

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Syntheses of 5-*O*-β-D-xylopyranosyl-L-arabinose and of 6-*O*-β-D-xylopyranosyl-D-galactose are described.

IN recent years several new disaccharides and oligosaccharides have been isolated from the hydrolysis products of polysaccharides.[1] The proof of the structure of these oligosaccharides depends in the main on degradative evidence. The purpose of this paper is to describe the synthesis of two disaccharides, one of which has been isolated by hydrolysis of cholla gum.[2] The second disaccharide has not yet been isolated from natural products, but the corresponding residue may be present as part of polysaccharides such as cherry and damson gum.[3] Both disaccharides were prepared by the Koenigs–Knorr[4] procedure. This method has been discussed in detail by Evans, Reynolds, and Talley[5] who also list many disaccharides which have been prepared by this or other methods. The principal product is the β-D-xyloside when acetobromo-D-xylose reacts with another sugar derivative. This acetobromo-derivative condenses with the more reactive primary

[1] Cf. Whistler and McGilvray, *J. Amer. Chem. Soc.*, 1955, **77**, 1884; Andrews and Jones, *J.*, 1954, 4134.
[2] Andrews, Ball, and Jones, *J.*, 1953, 4090.
[3] Hirst and Jones, *J.*, 1938, 1174.
[4] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.
[5] Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27.

alcohol group of methyl-L-arabofuranoside,[6] to yield the glycoside of the 1→5-linked disaccharide. The glycosidic methyl group, which was attached to the arabofuranose ring was removed under relatively mild conditions, to yield the non-crystalline reducing sugar, 5-*O*-β-D-xylopyranosyl-L-arabinose. This was chromatographically indistinguishable from a disaccharide isolated from cholla gum.[2] The derived phenylosazones were also indistinguishable. On reduction with sodium borohydride [7] the disaccharide gave an L-arabitol derivative which yielded a crystalline hepta-acetate. A derivative with identical physical properties was prepared from the disaccharide which had been isolated from cholla gum.[2] The synthesis of 2-*O*-β-D-xylopyranosyl-L-arabinose has been recently described.[8]

Acetobromo-D-xylose was condensed with 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose, yielding a disaccharide derivative. In order to destroy the excess of acetobromo-D-xylose the reaction mixture was boiled with sodium hydroxide solution, cooled, and de-ionised. Hydrolysis of the *iso*propylidene residues was carried out by hot dilute acetic acid. The resulting mixture of mono- and di-saccharides was fractionated on a cellulose column, from which 6-*O*-β-D-xylopyranosyl-D-galactose was obtained crystalline. Its optical rotation (−3·6°) indicates that according to Hudson's rule [9] the two sugars are linked by a β-glycosidic linkage. The mode of synthesis of the disaccharide proves that the glycosidic linkage is linked through position 6 of the galactose residue.

Experimental

Paper chromatography was carried out by the descending method [10] on Whatman No. 1 filter paper, the following solvents being used: (*a*) butan-1-ol–ethanol–water (3 : 1 : 1), (*b*) butan-1-ol–pyridine–water (10 : 3 : 3), (*c*) ethyl acetate–acetic acid–water (9 : 2 : 2), and (*d*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4) (all v/v). The positions of sugars on chromatograms were determined by spraying them with silver nitrate in acetone, followed by sodium hydroxide in ethanol,[11] or with *p*-anisidine hydrochloride in butan-1-ol.[12] The rates of movement of the sugars are quoted relative to that of galactose (R_{gal}) on the same chromatogram. Optical rotations were determined at 23° ± 3° and, unless otherwise stated, aqueous solutions were used, and the figures quoted are equilibrium values. Solvents were removed under reduced pressure.

Condensation of Acetobromo-D-xylose with Methyl αβ-L-Arabofuranoside.—To a solution of methyl L-arabofuranosides (3·28 g., 0·02 mole) in dry chloroform (50 ml.) there were added Drierite (20 g.), silver oxide (10 g.), iodine (1 g.), and glass beads. The mixture was shaken in a brown glass bottle for 30 min. to dry the reagents. A solution of acetobromo-D-xylose (6·78 g., 0·02 mole) in dry chloroform was then added and shaking was continued. After 24 hr., a test for ionisable bromine was negative. The mixture was then filtered and the filtrate concentrated to a clear yellow syrup. On paper chromatography the major component was noted to yield a predominant, elongated spot, which moved at twice the speed of rhamnose in solvent (*a*) and strongly reduced the silver nitrate spray but gave only a faint reddish-brown colour with the *p*-anisidine hydrochloride reagent. It was distinct from methyl α- or β-L-arabofuranoside. The syrup was dissolved in methanol, cooled, treated with 0·2M-sodium methoxide in methanol (2 ml.), stored at 0° overnight, and neutralised with cold dilute sulphuric acid. Solids were removed at the centrifuge and the clear solution was concentrated to a syrup. The glycosidic methyl group was removed by 10% formic acid at 90° in 1 hr. Formic acid was then removed by repeated evaporation with the intermediate addition of water. (In a second preparation the condensation was carried out in dioxan in place of chloroform.) The syrupy product, obtained after removal of insoluble salts and solvent, was boiled with an excess of sodium hydroxide in methanol for 7 hr. to deacetylate the product and destroy the excess of reducing xylose derivatives. After filtration the product was de-ionised (Amberlite resins

[6] Baker and Haworth, *J.*, 1925, **127**, 365.
[7] Wolfrom and Wood, *J. Amer. Chem. Soc.*, 1951, **73**, 2733; Abdel-Akher and Smith, *ibid.*, 4691.
[8] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 819.
[9] Hudson, *J. Amer. Chem. Soc.*, 1916, **38**, 1566.
[10] Partridge, *Biochem. J.*, 1948, **42**, 238.
[11] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[12] Hough, Jones, and Wadman, *J.*, 1950, 1702.

IR-120 and IR-4B) and concentrated to a syrup. This material contained glycosides which were converted into the reducing sugars by 0·01N-sulphuric acid at 90° in 12 hr. After cooling, the solution was neutralised and then concentrated.

The syrupy products from the above two preparations were combined and a portion of the mixture was fractionated on a charcoal column.[13] Elution first with water and then with increasing concentrations of ethanol gave fractions which contained monosaccharides (1·15 g.) and disaccharides: mixtures A (1·63 g.), B (0·48 g.), and C (1·19 g.).

Fraction A contained components with R_{gal} 0·85 and 1·05 (in solvent *a*), 0·9 and 1·3 (in solvent *b*).

The component of R_{gal} 1·05 (solvent *a*) was indistinguishable from 5-*O*-β-D-xylopyranosyl-L-arabinose on paper chromatograms. Fraction A was refractionated on four sheets of filter paper (Whatman No. 3 MM) (solvent *a*). The components were located by means of guide strips and the fractions isolated in the usual way.[14] Fraction A1 (0·05 g.) was a mixture and was not investigated. Fraction A2 (0·25 g.) contained a major component which had R_{gal} 0·85 (solvent *a*) and $[\alpha]_D$ +35° (*c* 4·98). Fraction A3 (0·36 g.) was composed of a sugar which moved faster than galactose (R_{gal} 1·05) and had $[\alpha]_D$ −41° (*c* 2·88). Fraction A4 (0·10 g.) was a mixture.

A sample of Fraction A3 was chromatographically indistinguishable from the required disaccharide, and its optical rotation (−41°) was in fair agreement with that recorded (−34°). In order to verify the identification the synthesised disaccharide was converted into the crystalline hepta-acetate of 5-*O*-β-D-xylopyranosyl-L-arabitol: A portion of the syrup (65 mg.) was dissolved in water and to the solution was added sodium borohydride (15 mg.) in water. After 2 days, reduction was complete. The solution was acidified with acetic acid and de-ionised on exchange resins. The filtrate was concentrated to a syrup which was acetylated with pyridine (3 ml.) and acetic anhydride (2 mg.) in the usual way. The product recrystallised from ethanol and then had m. p. 96—96·5°. This material showed no depression of m. p. on admixture with an authentic sample which was prepared from the cholla gum disaccharide and had $[\alpha]_D$ −62° (*c* 1·9 in $CHCl_3$). The synthetic *acetate* had $[\alpha]_D$ −61° (*c* 2·3 in $CHCl_3$) (Found: C, 50·0; H, 6·0; OAc, 52·0. $C_{24}H_{34}O_{16}$ requires C, 49·8; H, 5·9; OAc, 52·1%).

Condensation of Acetobromo-D-xylose and 1 : 2-3 : 4-*Di*-O-iso*propylidene-D-galactose.*—1 : 2-3 : 4-Di-*O*-*iso*propylidene-D-galactose (2·6 g., 0·01 mole), which had been purified through its crystalline 6-toluene-*p*-sulphonate, was dissolved in purified dioxan (25 ml.) in a dark brown glass bottle and Drierite (10 g.), silver oxide (5 g.), and glass beads were added. The mixture was shaken for 1 hr. and acetobromo-D-xylose (6·78 g., 0·2 mole), in dioxan (20 ml.), and iodine (0·5 g.) were then added and shaking was continued. After 13 hr. a test for ionisable bromine was negative. The mixture was filtered and the filtrate concentrated to a colourless syrup. This was boiled with a solution of potassium hydroxide (25% w/v) in methanol (15 ml.) for 3 hr. The dark brown solution was diluted with water, then filtered, and the filtrate de-cationised on Amberlite IR-120 resin. The acidic effluent (300 ml.) was heated at 80° for 4 hr. in order to hydrolyse *iso*propylidene groups and then de-ionised by passage through a column of Amberlite resin IR-4B. Concentration of the neutral effluent gave a syrup (2·27 g.) which consisted of galactose, a trace of xylose, and two substances with (i) R_{gal} 0·48 (solvents *a* and *b*) and 0·42 in solvent (*c*) and (ii) R_{gal} 0·56 (solvents *a* and *b*) and 0·50 in solvent (*d*). A portion of the above syrup was fractionated at 41° on a cellulose column which was irrigated with butan-1-ol saturated with water at 41°[15] and yielded four fractions. Fraction 1 (0·08 g.) contained the faster-moving compound. It was not identified. Fractions 2 (0·35 g.), 3 (0·90 g.), and 4 (0·06 g.) contained mainly the slower-moving *disaccharide*. Fraction 2 crystallised and fractions 3 and 4 also crystallised on nucleation. The crystalline product was recrystallised from moist methanol. The yield was 0·20 g., the m. p. 194—196°, and $[\alpha]_D$ −23·6° (5 min.) ⟶ −3·6° (2 hr., const.) (*c* 2·5) (Found: C, 42·1; H, 6·6. $C_{11}H_{20}O_{10}$ requires C, 42·2; H, 6·4%). The product on hydrolysis with hot dilute acid gave equal amounts of galactose and xylose.

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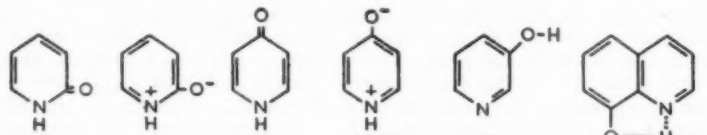
[13] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[14] Flood, Hirst, and Jones, *J.*, 1948, 1679.
[15] Counsell, Hough, and Wadman, *Research*, 1951, **4**, 143.

980. *The Tautomerism of* N-*Heteroaromatic Hydroxy-compounds. Part I. Infrared Spectra.*

By S. F. Mason.

The infrared spectra of a number of *N*-heterocyclic hydroxy-compounds have been measured in the O–H, N–H, and double-bond stretching-vibration regions. The compounds with a hydroxyl group α or γ to a ring-nitrogen atom absorb in the N–H and C:O stretching vibration regions both in the solid state and in chloroform solution, and so possess principally amide structures under these conditions. The remaining compounds have mainly enolic structures in solution, showing absorption due to a free or an intramolecularly hydrogen-bonded O–H group. The infrared evidence for the zwitterionic structure of the latter group of compounds in the solid state is discussed. The compounds which tautomerise to an amide with a quasi-*o*-quinonoid structure (*e.g.*, I) show an N–H stretching vibration absorption in the range 3360—3420 cm.$^{-1}$, whilst their quasi-*p*-quinonoid isomers (*e.g.*, II) absorb in the range 3415—3445 cm.$^{-1}$, and their analogues with five-membered rings (*e.g.*, VIII) in the range 3440—3485 cm.$^{-1}$. The position of the C:O band of such compounds depends upon the structural type and the number of nitrogen atoms in the ring carrying the potentially tautomeric hydroxyl group. For nuclei similarly substituted, the C:O band of the quasi-*o*-quinonoid amides lies at a higher frequency than that of the quasi-*p*-quinonoid isomers. The structures of some dihydroxy- and polyaza-compounds are elucidated by means of these correlations.

It has been shown by infrared spectroscopy that 2- and 4-hydroxy-pyridine,[1,2] -pyrimidine,[3] and -quinazoline,[4] and 2-hydroxyquinoline,[2] exist predominantly as amide forms in the solid state. In the present work an infrared study has been made of a wide range of such *N*-heterocyclic hydroxy-compounds, in the solid state and in chloroform and carbon tetrachloride solution. The results (Table 1) show that in solution all the compounds with a hydroxyl group α or γ to a ring-nitrogen atom absorb in the amide C:O (1630—1780 cm.$^{-1}$) [5] and N–H (3360—3500 cm.$^{-1}$) [5] stretching vibration regions. They exist, therefore, mainly in amide forms (*e.g.*, I or II respectively) in solution. The compounds with a hydroxyl group which is neither α nor γ to a ring-nitrogen atom give rise in solution (Table 2) to a sharp band near to 3600 cm.$^{-1}$, due to a free O–H stretching vibration or, if the hydroxyl group is *peri* to a ring-nitrogen atom, to a broad band in the range 3395—3470 cm.$^{-1}$, due to an intramolecular hydrogen-bonded O–H stretching vibration. The latter bands have widths at half-extinction of 60—100 cm.$^{-1}$ in dilute solution, whilst the compounds with amide structures give N–H bands with half-widths of 15—30 cm.$^{-1}$ under



(Ia) (Ib) (IIa) (IIb) (III) (IV)

the same conditions, allowing the two types to be distinguished. The compounds with a hydroxyl group which is neither α nor γ to a nitrogen atom do not absorb in the amide

[1] Sensi and Gallo, *Ann. Chim.* (*Italy*), 1954, **44**, 232.
[2] Gibson, Kynaston, and Lindsey, *J.*, 1955, 4340.
[3] Brown and Short, *J.*, 1953, 331; Brown, Hoerger, and Mason, *J.*, 1955, 211.
[4] Culbertson, Decius, and Christensen, *J. Amer. Chem. Soc.*, 1952, **74**, 4834.
[5] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954; "Chemical Applications of Spectroscopy," ed. W. West, Technique of Organic Chemistry, Vol. IX, Interscience, New York, 1956.

TABLE 1. *The infrared spectra of α- and γ-hydroxy-N-heteroaromatic compounds in the* N–H, O–H, *and* C=O *stretching vibration regions. Values in italics refer to carbon tetrachloride solution; the other solution values refer to chloroform as solvent.* (s = *strong* m = *medium*, w = *weak*.)

		N–H stretching frequencies (cm.$^{-1}$)		C=O stretching frequencies (cm.$^{-1}$)	
No.	Compound	In soln.	In the solid state	In soln.	In the solid state
	(I) *α-Hydroxy-compounds with six-membered ring systems.*				
1	2-Hydroxypyridine	*3404*, 3398	3198 m, 3165 s	1654	1650 s
2	2-Hydroxypyrazine	*3399*, 3393	3257 m, 3166 s	1730	1710 s, 1662 s
3	3-Hydroxypyridazine	*3394*, 3387	3237 m, 3194 s	1681	1678 s, 1652 s
4	2-Hydroxypyrimidine	*d* 3394	3195 m	1765	1733 m, 1647 s
5	2-Hydroxyquinoline	*3394*, 3386	3280 w, 3252 m	1656	1648 s
6	1-Hydroxy*iso*quinoline	*3418*, 3411	3278 w, 3150 s	1658	1653 s
7	3-Hydroxycinnoline	*3371*, 3367	3288 w, 3220 m	1660	1660 s
8	1-Hydroxyphthalazine	*3408*, 3401	3292 w, 3240 m	1674	1658 s
9	2-Hydroxyquinoxaline	*3391*, 3384	3290 w, 3258 m	1673	1690 m, 1642 s
10	8-Hydroxy-1 : 7-naphthyridine	*d* 3403	3308 w, 3095 s	1665	1693 s
11	5-Hydroxy-1 : 4 : 6-triazanaphthalene	*d* 3401	3330 w, 3145 s	1687	1692 s, 1650 s
12	9-Hydroxyphenanthridine	*3411*, 3402	*e*	1669	*e*
	(II) *α-Hydroxy-compounds with five-membered ring systems.*				
13	2-Hydroxybenziminazole	*3481*, 3469	*e*	1722	1728 s
14	2-Hydroxyimidazo[4 : 5-*b*]pyrazine	*d* 3441	*e*	1752	*e*
15	8-Hydroxy-7-methylpurine [a]	*3456*, 3444	*e*	1739	1742
16	8-Hydroxy-9-methylpurine [a]	*3465*, 3450	*e*	1744	1745
	(III) *γ-Hydroxy-compounds.*				
17	4-Hydroxypyridine	3442	3200 m, 3104 s	1638	1638 s
18	4-Hydroxypyridazine	*3438*, 3430	3288 m, 3078 m	1662	1660 m, 1640 s
19	4-Hydroxyquinoline	*3442*, 3438	3226 m, 3140 m	1645	1638 s
20	4-Hydroxycinnoline	*3427*, 3422	3222 m, 3190 s	1638	1610 s
21	8-Hydroxy-1 : 4 : 5-triazanaphthalene	*d* 3415	3198 w, 3173 m	1631	1625 s
22	5-Hydroxy-4-methylacridine	*3439*, 3434	*e*	1633	*e*
23	4-Hydroxy-2-methylbenzo[*g*]quinoline	*3443*, 3436	*e*	1645	*e*
24	4-Hydroxy-2-methyl-1 : 10-phenanthroline	*3389*, 3374	*e*	1634	*e*
	(IV) *αγ-Dihydroxy- and αγ-diaza-compounds.*				
25	4-Hydroxypyrimidine	*3395*, 3390	3257 m, 3200 s	1721	1716 m, 1684 s
26	2 : 4-Dihydroxy-1-methylpyrimidine	*d* 3395	*e*	1713, 1689	*e*
27	2 : 4-Dihydroxy-3-methylpyrimidine	*d* 3432	*e*	1717, 1661	*e*
28	4-Hydroxyquinazoline	*3402*, 3397	3365 w, 3205 s	1681	1663 s
29	4-Hydroxy-1 : 3 : 5-triazanaphthalene	*d* 3389	3177 m, 3095 s	1746	1710 s, 1670 s
30	6 : 7-Diethyl-4-hydroxypteridine [b]	*3401*, 3387	*e*	1685	*e*
31	6 : 7-Diethyl-2 : 4-dihydroxypteridine	*3421*, 3412 *3408*, 3395	*e*	1719, 1687	*e*
32	6-Hydroxy-7-methylpurine [a]	*d* 3390	*e*	1702	1697
33	6-Hydroxy-9-methylpurine [a]	*d* 3388	*e*	1711	1679
	(V) *Related compounds.*				
34	2-Pyrrolidone [c]	*3505*	3225	*1706*	1690
35	2-Piperidone [c]	*3425*	3236, 3096	*1672*	1669
36	Phthalimide	*3443*, 3431	*e*	1778, 1739	*e*
37	Homophthalimide	*3389*, 3383	*e*	1699	*e*

[a] Quoted from Brown and Mason (*J.*, 1957, 682). [b] Quoted from Brown and Mason (*J.*, 1956, 3443). [c] Quoted from Mecke and Mecke (*Chem. Ber.*, 1956, **89**, 343). [d] Insufficiently soluble. [e] Not measured.

C:O range (Table 4). Accordingly, these compounds possess enolic structures (*e.g.*, III and IV) in solution, even where tautomerism to vinylogous amide forms is possible (*e.g.*, V; R = H).

In the solid state the compounds with a hydroxy-group α or γ to a ring-nitrogen atom

give rise to an amide C:O band, which in general, but not invariably, is at a lower frequency than in solution (Table 1). Saturated cyclic and open-chain amides [5] show a similar lowering, which has been ascribed to hydrogen-bonding [6] or to dipole–dipole interaction [7] in the solid state. The fact that, in some cases, the C:O frequency is greater in solution than in the solid state favours the hypothesis of dipole–dipole interaction, as

TABLE 2. *The infrared spectra of enolic* N-*heterocyclic hydroxy-compounds in the* O–H *and double-bond stretching vibration regions.* (s = *strong*, m = *medium*, w = *weak*, b = *broad*.)

No.	Compound	O–H stretching frequencies ($cm.^{-1}$) In CCl_4 soln.	O–H stretching frequencies ($cm.^{-1}$) In the solid state	Double-bond stretching frequencies in the solid state ($cm.^{-1}$)
38	3-Hydroxypyridine	3595	2925—2500 m + b	1573 s, 1476 s
39	3-Hydroxyquinoline	3591	2942—2525 m + b	1598 s, 1469 s
40	5-Hydroxyquinoline	3599	2945—2550 m + b	1616 m, 1580 s
41	6-Hydroxyquinoline	3601	2960—2500 m + b	1633 w, 1577 s
42	7-Hydroxyquinoline	3597	2960—2525 m + b	1615 s, 1533 s
43	8-Hydroxyquinoline	3412 b	3180 s + vb	1577 s, 1507 s
44	4-Hydroxy*iso*quinoline	3603	2900—2500 m + b	1626 m, 1582 s
45	5-Hydroxy*iso*quinoline	3615	2950—2550 m + b	1623 m, 1588 s
46	6-Hydroxy*iso*quinoline	3610	2920—2620 m + b	1625 m, 1614 s
47	7-Hydroxy*iso*quinoline	3619	2900—2600 m + b	1628 m, 1589 s
48	8-Hydroxy*iso*quinoline	3611	2920—2550 m + b	1621 m, 1557 s
49	8-Hydroxycinnoline	3440 b	3100 s + vb	1624 m, 1582 m
50	6-Hydroxyquinazoline	3603	3125 s, 2933—2600 m + b	1640 m, 1582 s
51	8-Hydroxyquinazoline	3440 b	3145 s + vb	1624 m, 1592 s
52	5-Hydroxyquinoxaline	3470 b	3418 m, 3322 s, 3225 m	1625 m, 1583 s
53	6-Hydroxyquinoxaline	3596	2950—2500 m + b	1618 s, 1522 s
54	8-Hydroxy-1 : 6-naphthyridine	3456 b	3314 m, 3245 s, 3125 s	1614 m, 1578 m
55	2-Hydroxyphenanthridine	3617	2922—2532 m + b	1614 s, 1574 m
56	6-Hydroxyphenanthridine	3607	2892—2590 m + b	1628 m, 1605 s
57	7-Hydroxyphenanthridine	3613	2923—2549 m + b	1627 m, 1574 s
58	1-Hydroxyacridine	3398 b	*a*	*a*
59	3-Hydroxyacridine	3611	*a*	*a*
60	4-Hydroxyacridine	3607	*a*	*a*
61	1-Hydroxyphenazine	3448 b	*a*	*a*
62	2-Hydroxyphenazine	3602	*a*	*a*
63	6-Hydroxy-1 : 7-phenanthroline	3395 b	*a*	*a*

[a] Not measured.

TABLE 3. *The infrared spectra, in the solid state, of some* N-*heteroaromatic hydroxy-compounds insoluble in chloroform, in the* N–H, O–H, *and double-bond stretching vibration regions.* (s = *strong*, m = *medium*, w = *weak*, b = *broad*.)

No.	Compound	N–H or O–H stretching frequencies ($cm.^{-1}$)	Double-bond stretching frequencies ($cm.^{-1}$)
64	2 : 4-Dihydroxypyridine	3230 w, 2915—2520 m + b	1661 s, 1635
65	5-Hydroxypyrimidine	2922—2532 m + b	1608 s, 1568 s
66	2 : 4-Dihydroxyquinoline	3250 w, 2908—2525 m + b	1662 s, 1628 s
67	4 : 8-Dihydroxyquinoline	3340 s, 2880—2530 m + b	1621 s, 1570 s
68	5-Hydroxycinnoline	2921—2555 m + b	1621 m, 1579 s
69	6-Hydroxycinnoline	3145 w, 2875—2600 m + b	1640 m, 1590 s
70	7-Hydroxycinnoline	2915—2620 m + b	1622 s, 1565 s
71	6-Hydroxyphthalazine	3372 m, 3264 s	1649 m, 1618 s
72	2-Hydroxyquinazoline	3313 w, 3194 s	1680 s, 1608 s
73	4-Hydroxy-1 : 5-naphthyridine	3203 w, 3108 m	1624 s, 1586 m

the C:O frequency could be increased by hydrogen-bonding only if the C:O···H angle were $<90°$, a configuration which is unfavourable for hydrogen-bonding. In most of the cases (compounds 9, 10, 11, 15, 16) N–H···N hydrogen-bonding might allow weak ancillary N–H···O hydrogen-bonding with a C:O···H angle $<90°$ (*e.g.*, VI), but such bonding would not be possible in the case of 2-hydroxybenziminazole (VIII).

[6] Krimm, *J. Chem. Phys.*, 1955, **23**, 1371.
[7] Cannon, *Mikrochim. Acta*, 1955, 555; *J. Chem. Phys.*, 1956, **24**, 491.

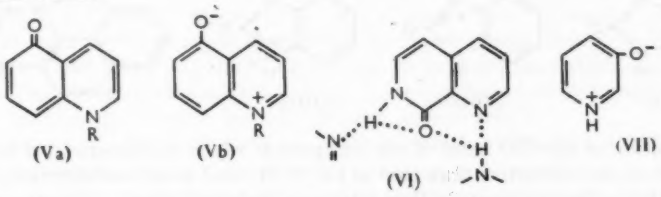
The N–H and O–H bands of *N*-heterocyclic hydroxy-compounds in the solid state fall into three general classes (Table 1, 2, and 3). The α- and γ-hydroxy-compounds absorb mainly in the range 3100—3300 cm.$^{-1}$, the bands being sharp, whilst the *peri*-compounds give very broad bands in the same region, and the remainder show broad bands between 2450 and 2950 cm.$^{-1}$. Empirical correlations have been established between the X–H···Y distance (R) of intermolecular hydrogen-bonds and the frequency shift ($\Delta\nu$) of the X–H stretching vibration absorption.[8,9] O–H···O absorptions fall off rapidly with decreasing distance according to the relation: [8]

$$\Delta\nu = 4{\cdot}43 \times 10^3(2{\cdot}84 - R)$$

whilst N–H···O absorptions fall off more slowly, following the relation: [8]

$$\Delta\nu = 0{\cdot}548 \times 10^3(3{\cdot}21 - R)$$

It is probable, therefore, that α- and γ-hydroxy-compounds are N–H···O hydrogen-bonded with distances of 2·6—3·0 Å between the bonded centres, whilst the remainder, apart from the *peri*-hydroxy-compounds, are O–H···O hydrogen-bonded with distances of 2·56—2·72 Å between the bonded centres. Some polyaza-members of the latter group absorb above 3100 cm.$^{-1}$ (compounds 50, 69, and 71, Tables 2 and 3) and may be also O–H···N hydrogen-bonded, as this bond absorbs at frequencies which fall slowly with decreasing bond distance.[9] The *peri*-hydroxy-compounds may remain intramolecularly O–H···N hydrogen-bonded in the solid state, as they absorb in the range 3100—3200 cm.$^{-1}$ expected [9] for the calculated oxygen–nitrogen distance of 2·7 Å. However, intramolecular O–H···O bonds do not follow the frequency–bond distance relation established for intermolecular bonds.[9]



(Va) (Vb) (VI) (VII)

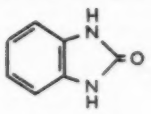
A zwitterion structure for 3-hydroxypyridine (VII) in the solid state has been proposed,[1] as it absorbs in the hydrogen-bonded $^+$N–H stretching vibration region of the amino-acids near 2000 cm.$^{-1}$. This is not good evidence for the structure (VII), since the nitrogen atom in the amino-acid zwitterions is in a sp^3 state of hybridisation, whilst in (VII), as in (I) and (V), it is in a sp^2 state. For quadricovalent nitrogen in a sp^3 state, the free N–H stretching frequency [9] is near 3100 cm.$^{-1}$, and the hydrogen-bonded frequencies [8] cover a range down to 2000 cm.$^{-1}$, whilst the corresponding frequencies for quadricovalent nitrogen in a sp^2 state may be expected to be close to those recorded in Table 1 for the compounds with amide structures. However, the *N*-heteroaromatic hydroxy-compounds in which the nitrogen and the oxygen atoms are not conjugated exist partly as zwitterions in aqueous solution,[10] and possibly also in the solid state. In the double-bond stretching vibration region the spectra of the hydroxyquinolines in the solid state, but not in solution, resemble those of the corresponding *N*-methyl derivatives with fixed zwitterionic structures (Tables 2 and 4). The bands observed are due to ring stretching modes which should be sensitive to structural changes, such as the tautomerism from enol to zwitterion, but 5- and 7-hydroxyquinoline do not absorb in the amide C:O region whilst their *N*-methyl derivatives, to the structure of which vinylogous amide forms contribute (*e.g.*, Va, R = Me), absorb in the C:O range (Tables 2 and 4).

[8] Pimentel and Sederholm, *Mikrochim Acta*, 1955, 639.
[9] Nakamoto, Margoshes, and Rundle, *J. Phys. Chem.*, 1955, **77**, 6480.
[10] Part II, following paper.

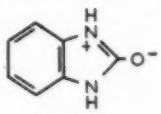
TABLE 4. *The infrared spectra, in chloroform solution, of the enolic hydroxyquinolines and their* N*-methyl derivatives (zwitterionic forms) in the double-bond stretching vibration region.*

No.	Compound	Frequencies ($cm.^{-1}$)	No.	Compound	Frequencies ($cm.^{-1}$)
39	3-Hydroxyquinoline	1614	42	7-Hydroxyquinoline	1621
74	1-Methyl- ,, ...	1592	77	1-Methyl- ,, ...	1639, 1598
40	5-Hydroxyquinoline	1619	43	8-Hydroxyquinoline	1628
75	1-Methyl- ,, ...	1648, 1573	78	1-Methyl ,, ...	1573
41	6-Hydroxyquinoline	1616			
76	1-Methyl- ,, ...	1583			

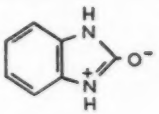
In solution the N–H bands of *N*-heteroaromatic hydroxy-compounds which tautomerise predominantly to amide forms fall into ranges, depending upon the structural type. The quasi-*o*-quinonoid amides (*e.g.*, I) absorb between 3360 and 3420 $cm.^{-1}$, whilst their quasi-*p*-quinonoid isomers (*e.g.*, II) absorb between 3415 and 3445 $cm.^{-1}$ and their analogues with five-membered rings (*e.g.*, VIII) between 3440 and 3485 $cm.^{-1}$ (Table 1). Aza-substitution in any of the three structural types lowers the N–H stretching frequency, so that there is some overlap of the ranges, but the mono- and di-aza-members of each type absorb over more restricted and distinct regions (Table 1). An exception is 4-hydroxy-2-methyl-1 : 10-phenanthroline which absorbs at a lower frequency than the other diaza-members of the quasi-*p*-quinonoid type (Table 1), owing to intramolecular hydrogen-banding (IX). The N–H band of this compound has a width at half-extinction of 25 $cm.^{-1}$, and so it cannot be distinguished from the free N–H absorption of the quasi-*o*-quinonoid amides by its width (see above).



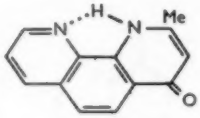
(VIIIa)



(VIIIb)



(VIIIc)



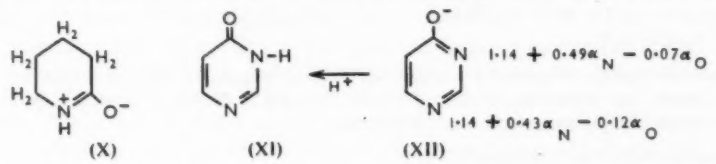
(IX)

The position of the C:O band of the compounds which tautomerise predominantly to amide forms is more sensitive than that of the N–H band to aza-substitution, particularly to substitution in the ring carrying the tautomeric hydroxyl group. The quasi-*o*-quinonoid amides with not more than one nitrogen atom in the ring substituted by the hydroxyl group give a C:O band in the range 1654—1687 $cm.^{-1}$, whilst the corresponding quasi-*p*-quinonoid amides absorb between 1630 and 1645 $cm.^{-1}$ in solution (Table 1). The high frequency of the C:O band and the low frequency of the N–H band of the quasi-*o*-quinonoid amides, relative to their quasi-*p*-quinonoid isomers, may be ascribed to an inducto-electromeric effect between the atoms of the amide group. The nitrogen atom enhances the electronegativity of the carbon atom of the C:O group, and so increases the double-bond character of that group, whilst the nitrogen atom becomes positively charged by the inductive effect of the oxygen atom. In general, the stretching frequency of the N–H group falls as the nitrogen atom becomes more positively charged, indole,[11] for example, absorbing at 3484 $cm.^{-1}$ and purine [12] at 3441 $cm.^{-1}$ in chloroform solution. In the three structural types of amide, positive charge on the N–H group arises also by resonance (*e.g.*, between Ia and b; IIa and b; VIIIa, b, and c). The charge is localised in the six-membered ring compounds, but it is shared with another N–H group in the five-membered ring amides, and the stretching frequency of the N–H group is higher in the latter compounds than in the former. Ring strain may also contribute, as the frequency of the N–H absorption is higher in 2-pyrrolidone than in 2-piperidone (Table 1). In both the N–H and C:O regions 2-piperidone absorbs at higher frequencies than its aromatic analogue, 2-hydroxypyridine (Table 1), indicating that the zwitterion resonance form (Ib), in which the aromatic

[11] Mason, unpublished results.
[12] Brown and Mason, *J.*, 1957, 682.

resonance is preserved, contributes more to the structure of the latter than the corresponding form (X) to the structure of the former.

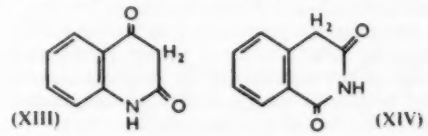
The correlations established above may be used to determine the structure of *N*-heterocyclic hydroxy-compounds which may tautomerise to more than one amide form.[12, 13] In the cases of 4-hydroxy-pyrimidine, -quinazoline, -1 : 3 : 5-triazanaphthalene, and -pteridine, and 6-hydroxy-7-, and -9-methylpurine, a tautomeric hydroxyl group is placed both α and γ to a ring-nitrogen atom, and they may form either quasi-*o*- or quasi-*p*-quinonoid amides. The N–H band of these compounds lies in the range characteristic of the quasi-*o*-quinonoid amides (Table 1), and thus they have the structure of that type (*e.g.*, XI). This conclusion is supported by ultraviolet spectroscopy for the cases of 4-hydroxy-pyrimidine,[3] -quinazoline,[14] and -pteridine,[13] though it is surprising in view of the classical generalisation that *p*-quinonoid structures are more stable than isomeric *o*-quinonoid structures. However, the molecular-orbital theory indicates that, granted certain assumptions, the structure of 4-hydroxypyrimidine should be (XI). Considered as a perturbed benzyl anion, the anion of 4-hydroxypyrimidine has the charge distribution (XII), where α_N and



(X) (XI) (XII)

α_O are the differences between the Coulomb integrals of the nitrogen and oxygen atoms respectively and the Coulomb integral of carbon, in terms of the C:C resonance integral, β. A proton will bond to the nitrogen atom with the higher charge density in the anion of 4-hydroxypyrimidine, namely to the 3-, rather than to the 1-nitrogen atom, if α_N is positive and α_O has a positive or small negative value. These conditions are reasonable in view of the relative electronegativities of carbon, nitrogen, and oxygen.[15]

2 : 4-Dihydroxy-pyridine and -quinoline, with hydroxyl groups both α and γ to a ring nitrogen atom, may tautomerise to quasi-*o*- or -*p*-quinonoid amides, or to keto-amides (*e.g.*, XIII). These compounds are insufficiently soluble in chloroform to give infrared spectra in solution, but in the solid state they give two bands in the double-bond region, one in the range of the monoaza-*o*-quinonoid amides, and the other in, or near to, the range for the quasi-*p*-quinonoid isomers (Table 3). It is probable, therefore, that in the solid state both quasi-*o*- and -*p*-quinonoid amide forms occur in these compounds. The ultraviolet evidence indicates that for 2 : 4-dihydroxypyridine the quasi-*o*-quinonoid amide form predominates in aqueous solution.[16] Tautomerism to the keto-amide does not occur, as (XIII) should absorb [5] between 1680 and 1700 cm.$^{-1}$. Homophthalimide absorbs in this range, but not in the O–H stretching vibration region in solution (Table 1), and therefore possesses the analogous structure (XIV). 4 : 8-Dihydroxyquinoline in the



(XIII) (XIV)

solid state does not absorb strongly in the double-bond region above 1621 cm.$^{-1}$ (Table 3), a frequency rather low for an amide C:O vibration, and near to a ring-stretching vibration in quinoline itself [11] at 1620 cm.$^{-1}$. Tautomerism to the amide form may be suppressed in

[13] Brown and Mason, *J.*, 1956, 3443.
[14] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[15] Pritchard and Skinner, *Chem. Rev.*, 1955, **55**, 745.
[16] Den Hertog and Buurman, *Rec. Trav. chim.*, 1956, **75**, 257.

this case by intramolecular hydrogen-bonding between the 8-hydroxy-group and the ring-nitrogen atom.

EXPERIMENTAL

Infrared Spectra.—These were measured with a Perkin-Elmer model 12C spectrometer with a lithium fluoride prisms for the O–H and N–H stretching vibration regions and a sodium chloride prism for the double-bond stretching vibration region. The compounds were examined at concentrations of 10^{-2} to 10^{-3}M in cells of 5 cm. (CCl_4) or 1 cm. ($CHCl_3$) thickness in the O–H and N–H regions, and 1 mm. in the double-bond region, and as solids included in pressed potassium bromide discs. Band half-widths were measured at a constant slit width of 0·05 mm.

Molecular-orbital Calculation.—The list of atom–atom polarisabilities of the benzyl anion recorded by Jaffé [17] was used in calculations of the charge distribution in the anion of 4-hydroxypyrimidine. The 4 : 4 and 4 : 4′ polarisabilities in this list are incorrect in sign.

Materials.—5-, 6-, and 7-Hydroxycinnoline and 6-hydroxyphthalazine were kindly supplied by Dr. K. Schofield.[18] Homophthalimide, 1-hydroxyphthalazine, and 4-hydroxy*iso*quinoline by Professor N. B. Chapman, 5-hydroxypyrimidine by Dr. J. F. W. McOmie, 5-, 6-, 7-, and 8-hydroxy*iso*quinoline by Dr. R. A. Robinson,[19] 2-, 6-, and 7-hydroxyphenanthridine by Dr. M. M. Coombs, [20] 3- and 4-hydroxypyridazine by Dr. J. Druey, and 2-hydroxyimidazo-[4 : 5-*b*]pyrazine by Dr. H. T. Openshaw. The remaining compounds were kindly provided by Professor A. Albert.[21]

The author thanks Professor A. Albert for helpful discussion, Mr. D. Light for technical assistance, and the Australian National University for a Research Fellowship, during the tenure of which the present work was carried out.

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[17] Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.
[18] Osborn and Schofield, *J.*, 1956, 4207.
[19] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1939, 1942, 1944.
[20] Arcus and Coombs, *J.*, 1954, 4319.
[21] Albert and Phillips, *J.*, 1956, 1294.

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981. *Amine Oxidation. Part II.* Reactions of Aliphatic Tertiary Amines with Quinones. Detection of Dehydrogenation by the Formation of Coloured Dialkylaminovinylquinones.*

By D. BUCKLEY, SONIA DUNSTAN, and H. B. HENBEST.

This and the following papers are concerned with the oxidation of tertiary amines by organic oxidising agents, which often proceed readily at room temperature. In this paper structural factors influencing the reactions of tertiary amines with *p*-quinones are discussed. These reactions may proceed particularly readily owing to prior formation of molecular complexes, for which spectroscopic evidence is presented. Reactions between tertiary amines containing a flexible $\rangle N\cdot CH\cdot CH\langle$ grouping and some halogenated quinones can result in dehydrogenation to enamines $\rangle N\cdot C{:}C\langle$. If the enamine contains a β-CH grouping, coupling with a second molecule of halogenated quinone can occur, to give a blue or purple dialkylaminovinylquinone. From the viewpoint of the isolation of the coloured quinone the two-stage reaction proceeds best with simple *N*-ethyl compounds. Some of the properties of these new coloured quinones are described.

THE observation was made [1] that when triethylamine was added to a solution of chloranil in benzene, the mixture became green and then blue with the simultaneous precipitation of a colourless crystalline product. The compound responsible for the blue colour was

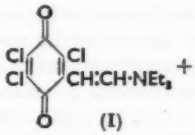
* Part I, *J.*, 1957, 3032.

[1] Cf. *Chem. and Ind.*, 1956, 1096; the initial observations were made by one of us (H. B. H.) in the Converse Memorial Laboratories, Harvard, where very generous facilities were placed at our disposal by Professor R. B. Woodward.

readily obtained crystalline (m. p. 131—132°), and the colourless product was shown to be triethylamine hydrochloride. The production of green or blue colours from aliphatic tertiary amines and chloranil has been recorded before.[2]

Analysis of the blue compound suggested the formula $(C_{12}H_{12}O_2NCl_3)_n$, corresponding, when $n = 1$, to the loss of one molecule each of hydrogen and of hydrogen chloride from a 1 : 1 reaction between the amine and the quinone. Molecular-weight determinations confirming this degree of complexity and the infrared absorption showing the presence of conjugated carbonyl groups, the blue compound was formulated as the diethylaminovinylquinone (I), the first member to be characterised of this group of coloured quinones.

(*a*) $C_6O_2Cl_4 + NEt_3 \longrightarrow CH_2{:}CH{\cdot}NEt_2 + C_6H_2O_2Cl_4$

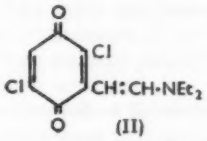
(*b*) $C_6O_2Cl_4 + CH_2{:}CH{\cdot}NEt_2 + NEt_3 \longrightarrow$  $+ NHEt_3Cl$

(I)

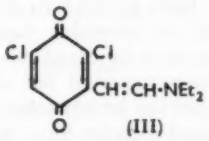
The formation of the blue quinone (I) is believed to take place in two steps. First (*a*), the amine is dehydrogenated to diethylvinylamine—in agreement, tetrachloroquinol was isolated from the final reaction solution. Secondly (*b*), the diethylvinylamine acts as a nucleophile, displacing chlorine from a second molecule of chloranil (cf. following paper). This second stage has an electronic analogy to the *C*-alkylation of β-dialkylaminocrotonic esters and cyclic enamines [3] by alkyl halides. The structure (I) for the blue quinone is confirmed by its properties (some of which are given at the end of this paper), and by the synthesis of this and related compounds by alternative methods (two following papers).

Scope of the Dehydrogenation–Coupling Reaction.—(i) *Quinone component.* The reaction between chloranil (a nearly saturated solution in benzene) and triethylamine (2·5 mol.) was complete within 24 hr. at 22° in the dark, the yield of blue quinone (based on above equations) being approx. 50%. Losses occurred during isolation, as spectroscopic examination of the reaction solution showed that more than 70% of the blue quinone was actually formed, the absorption of the blue quinone at 6400 Å (ε 8800 for the pure compound) being used for this computation. The reaction between bromanil and triethylamine was similar, the spectroscopic yield of the blue tribromo-analogue being 60%: again the reactivity of the coloured quinone resulted in losses during isolation. Under the same conditions iodanil did not react appreciably with triethylamine. This must be due to inhibition of the dehydrogenation step (*a*) (see below), as tests with diethylvinylamine generated by other methods (following papers) showed that the coupling reaction could occur with the iodo-quinone.

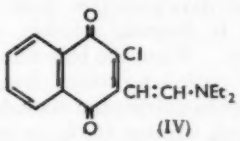
Other halogenated quinones gave lower yields of blue quinones than those obtained from chloranil and bromanil. Thus, low yields of the blue quinones (II) and (III) were obtained from 2 : 5- and 2 : 6-dichloro-*p*-benzoquinone (even allowing for the fact that the



(II)



(III)



(IV)

enamine is attacking CH positions on the quinones and hence more initial dichloroquinone is required in each case for oxidation of the intermediate condensation products to give the final blue quinones). 2-Chloro- and 2 : 3-dichloro-naphthaquinone reacted slowly

[2] Sivadjian, *Bull. Soc. chim. France*, 1935, **2**, 623; Stahl, *Analyt. Chem.*, 1953, **25**, 1725.
[3] Hamilton and Robinson, *J.*, 1916, 1029, 1038; Stork *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 2029; 1956, **78**, 5128.

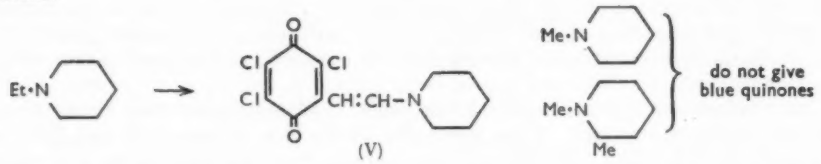
with triethylamine, giving a low yield of the purple quinone (IV) in each case: from the viewpoint of synthesis the method given in the following paper is much preferable.

Electron-donating methoxyl groups are known [4] to reduce the oxidation potentials of quinones and 2 : 5-dichloro-3 : 6- and 2 : 6-dichloro-3 : 5-dimethoxy-*p*-benzoquinone did not react appreciably with triethylamine in the dark [the former compound was chosen as a convenient detector for the dehydrogenation of triethylamine by other agents, as a methoxyl group is displaced by diethylvinylamine to give a blue quinone (two following papers)].

The reaction took another course when quinones containing adjacent unsubstituted positions were used. Black, apparently amorphous, materials separated (together with triethylamine hydrochloride) from the reactions of chloro- and 2 : 3-dichloro-*p*-benzoquinone with triethylamine in benzene at room temperature. The insolubility of these products indicated high molecular weights and analyses showed that several molecules of quinone to each molecule of amine were involved in their formation. No appreciable reaction took place between *p*-benzoquinone and triethylamine at room temperature in the dark, but, on heating, a similar insoluble black material separated.

No ready reaction occurred between triethylamine and *p*-toluquinone, α-naphthaquinone, or 2 : 5-dichloroanthraquinone and it may be concluded that the presence of halogen on the *p*-benzoquinone ring is necessary for oxidation at room temperature.

(ii) *Amine component.* Various tertiary amines were added to chloranil in benzene solution at room temperature in the dark. Judged by the rate of formation of blue colours, the reactions of tri-*n*-butylamine and *NN*-diethyl*cyclo*hexylamine with the quinone were slower than that of triethylamine. The blue product from tributylamine could not be purified satisfactorily owing to its reactivity; in general, alkyl substituents on the vinyl side-chain enhance the reactivity (*e.g.*, towards aqueous reagents) of the compounds. With 1-ethylpiperidine a blue colour developed, and the quinone (V) resulting from dehydrogenation of the ethyl group was isolated (an alternative synthesis is given in following paper). The difficulty of dehydrogenating the piperidine ring was confirmed by the non-production of blue quinones on treatment of 1-methylpiperidine and 1-methyl-α-pipecoline with chloranil [the coupling reaction can take place with the endocyclic enamine from the former amine (cf. Part III)]. 1-Methylpyrrolidine and nicotine behaved similarly in not giving blue quinones. Dimethyl*iso*propylamine (related in structure to 1-methyl-α-pipecoline) reduced chloranil slowly, but no blue quinone was obtained.



(V)

Simple dialkylanilines have long been known [5] to give *immediate* blue colours with chloranil in benzene solution, owing to reversible formation of molecular complexes (cf. below). When the blue solutions given by dimethyl- and diethyl-aniline were heated and then cooled, no colour changes were apparent but after each had been shaken with dilute acid to extract the dialkylanilines the former solution reverted to the yellow colour of chloranil, whereas the latter remained greenish-blue, indicating that some dehydrogenation of ethyl groups (and thence coupling) had taken place.

In tetramethylethylenediamine, $Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$, the group to be dehydrogenated is flanked by nitrogen on both sides. Chloranil was reduced by this amine but a blue quinone was not formed.

[4] Fieser, *J. Amer. Chem. Soc*, 1928, **50**, 439.
[5] Cf. Pfeiffer, " Organische Molekulverbindungen," Enke, Stuttgart, 1927.

The structure of *iso*butyldimethylamine $Me_2CH{\cdot}CH_2{\cdot}NMe_2$ permits dehydrogenation, but the absence of a CH group β to nitrogen in the resulting enamine $Me_2C{:}CH{\cdot}NMe_2$ prevents formation of a blue quinone. This amine reduced chloranil (more slowly than triethylamine), and the isolation of *iso*butyraldehyde 2 : 4-dinitrophenylhydrazone from the reaction solution indicated that the expected enamine was formed.

Another group to be considered consists of amines lacking an alkyl group β to nitrogen so that the formation of an enamine is impossible. The simplest compound of this type, trimethylamine, reduced chloranil more slowly than triethylamine, but the reaction has not been closely scrutinised. Attack on the central methylene group of tetramethylmethylenediamine $Me_2N{\cdot}CH_2{\cdot}NMe_2$ could be followed by the decrease in the yield of formaldehyde formed on hydrolysis. Under the chosen conditions the yield of formaldehyde had fallen to 50% after about 60 hr. The reactions of benzyldimethylamine $Ph{\cdot}CH_2{\cdot}NMe_2$ and tribenzylamine with chloranil were very slow at room temperature, and they were therefore studied in boiling benzene solutions. After 24 hr. the former amine had reduced about half of the quinone: addition of 2 : 4-dinitrophenylhydrazine reagent then gave the derivative of benzaldehyde (26% based on a 1 : 1 reaction between the quinone and amine). For tribenzylamine the yields of benzaldehyde 2 : 4-dinitrophenylhydrazone were determined after different times, a 60% yield being obtained after 60 hr.

Loss of hydrogen (overall as hydride) from dihydro-1-*p*-methoxyphenylpyridine (VI) [6] should receive encouragement from the simultaneous production of an aromatic pyridinium structure. The reaction between the amine and chloranil was very rapid at room temper-

(VI) $p\text{-}MeO{\cdot}C_6H_4{\cdot}NC_5H_6 + C_6O_2Cl_4 \longrightarrow [p\text{-}MeO{\cdot}C_6H_4{\cdot}NC_5H_5]^+[C_6HO_2Cl_4]^-$ (VII)

$\downarrow$ HCl

(VIII) $[p\text{-}MeO{\cdot}C_6H_4{\cdot}NC_5H_5]^+Cl^- + C_6H_2O_2Cl_4$

ature, a greenish precipitate separating. From its insolubility in benzene, its lack of infrared carbonyl absorption, and its conversion into the methoxyphenylpyridinium chloride (VIII) and tetrachloroquinol in good yields on treatment with dilute hydrochloric acid, this greenish compound appears to be a salt (cf. VII), although satisfactory analyses could not be obtained.

Mechanism(s) of the Tertiary-amine–Quinone Reactions.—On the simplest analysis, the oxidation level of enamine formation is reached by the transfer of hydride ion from the amine to the quinone, loss of a proton from the resulting conjugate acid of the enamine presumably being rapid and without influence on the rate, *e.g.*:

$$\text{>}N{\cdot}CH_2{\cdot}CH_2 \longrightarrow [\text{>}N{=}CH{\cdot}CH_2]^+ \xrightarrow{-H^+} \text{>}N{\cdot}CH{=}CH_2$$

or

$$\text{>}N{\cdot}CH_2Ph \longrightarrow [\text{>}N{=}CHPh]^+ \xrightarrow{H_2O} \text{>}NH + CHO{\cdot}Ph$$

For the formation of an enamine, hydride-ion transfer therefore represents the overall reaction, but not necessarily the rate-determining step for which a single-electron step (also occurring in a bimolecular process) must also receive consideration. Various possible steps in the reactions may be expressed as follows:

$$\text{Amine (A)} + \text{Quinone (Q)} \rightleftharpoons [AQ \longleftrightarrow A^+Q^-] \xrightarrow{\text{or}} [\text{A minus H}]\cdot + [QH]\cdot$$

$$\text{Enamine} \longleftarrow [\text{A minus H}]^+ + [QH]^-$$

Of simple functional groupings lacking possibilities for hydrogen bonding, tertiary amines are the most easily oxidised by quinones (and by many other reagents). The

[6] Karrer, Schwarzenbach, and Utzinger, *Helv. Chim. Acta*, 1937, **20**, 72.

relatively rapid rates of these reactions must clearly depend on favourable redox potentials (see below). A second factor in promoting the reactions with quinones may be initial (reversible) association of the reactants in the form of a molecular (charge-transfer) complex [7] represented as [AQ ⟷ A^+Q^-] in the above scheme. In other words, the initial (probably rate-determining) hydrogen-transfer step may be considered to take place within suitably activated complex molecules present in significant concentration.

The best evidence for the initial production of molecular complexes from tertiary amines and quinones comes from light-absorption measurements; complex formation is however often readily observed visually.

As stated already, many dialkylanilines give immediate blue colours with halogenated quinones, and in suitable cases the coloured complexes can be obtained crystalline. The complexes from trialkylamines apparently differ from those from dialkylanilines only in their lower stability and different absorption properties. Thus the immediate colour produced on adding a trialkylamine to a solution of chloranil in benzene is normally reddish-brown and, as with the blue complexes from dialkylanilines, treatment with dilute acid regenerates the original quinone and amine (salt). When suitably dilute solutions of pure reagents are used the initial reddish-brown colour from triethylamine and chloranil can be seen before the formation of the blue dialkylaminovinylquinone becomes apparent.

The available evidence suggests that the following structural factors promote the association of tertiary amines and quinones to molecular complexes (in which oxidation of the amine can take place if the redox potentials are suitable): (*a*) chlorine or bromine substituents on the *p*-benzoquinone ring, (*b*) an unsaturated (aromatic) ring linked directly to nitrogen in the amine, and (*c*) steric accessibility of the nitrogen atom. These factors are next discussed in turn.

(*a*) Earlier work [8] has shown that the presence of chlorine on the quinone ring enhances the stability of the complexes obtained with dimethylaniline, the more stable complex from chloranil absorbing more strongly and at a longer wavelength than that from *p*-benzoquinone (Beer's law not obeyed in either case). Some further measurements are now given in the following Table.

Absorption maxima (Å) *for complexes formed in benzene solutions,* 0·1M *in amine and in quinone* (*determined in a* 1 *mm. cell*).

Quinone	Amine		
	Me_3N	$N[-CH_2\cdot CH_2-]_3N$	$NPhMe_2$
p-Benzoquinone	—	No max. (orange-red)	No max.* (red)
2 : 6-Dichloro-*p*-benzoquinone	No max. (red)	5450 (purple)	5900 (blue)
Chloranil	No max. (red)	6000 (blue)	6500 (blue)

* In more concentrated solutions this complex gives a max. at 5050 Å.[6]

With dimethylaniline the two chlorinated quinones gave well-defined absorption maxima, whereas this amine and benzoquinone gave only enhanced general absorption at the concentrations studied.

These results parallel the chemical findings, the chloroquinones, but not benzoquinone, reacting with triethylamine at room temperature in dilute benzene solution.

As mentioned earlier, iodanil differs from its bromo- and chloro-analogues in not giving a blue dialkylaminovinylquinone on treatment with triethylamine. As the oxidation potentials of these quinones are very similar ($E°$ 0·737, 0·746, 0·742 v respectively), the lack of reactivity of iodanil appears to be caused by the bulkiness of the iodine atoms,

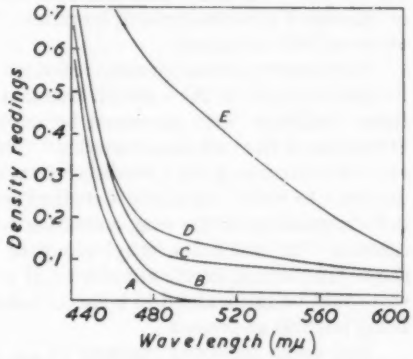
[7] For a recent review of charge-transfer complexes, see Orgel, *Quart. Rev.*, 1954, **8**, 422. Other references pertaining to quinones are given by Kuboyama and Nagatura, *J. Amer. Chem. Soc.*, 1955, **77**, 2644, and to charge-transfer complexes by Kosower, *ibid.*, 1956, **78**, 3493, 5700.

[8] Briegleb and Czekalda, *Z. Electrochem.*, 1954, **58**, 249.

preventing the necessary association with the trialkylamine for reaction to occur. The poorer association of chloranil with hexaethylbenzene than with hexamethylbenzene has also been attributed to steric factors.[9] In agreement, iodanil gave no appreciable immediate colour with dimethylaniline, whereas bromanil and chloranil gave blue colours. This may be expressed in a more general form, for quinones which dehydrogenate (say) triethylamine (and thence give coloured dialkylaminovinylquinones) are those which give immediate mauve to blue colours with dimethylaniline due to strong complex formation.

(*b*) The stabilising effect of an aromatic group attached to nitrogen can be seen by comparing the behaviour of dimethylaniline and trimethylamine with chloranil (Table). The dialkylaniline complex, which can easily be obtained crystalline, is represented by strong absorption near 6500 Å, whereas the complex from trimethylamine cannot be isolated at room temperature and gives a relatively weak general absorption.

(*c*) Steric factors for the amine component were investigated by adding various trialkylamines to a standard solution of chloranil and recording the changes of absorption in the 4500—6000 Å region (Figure), which correspond to the reddish-brown colours observed immediately with more concentrated solutions. The absorption due to complex formation



Absorption (0·2 cm. cell) of chloranil (0·04M) with (A) no additive, (B) tribenzylamine (0·09M), (C) tri-n-propylamine (0·08M), (D) 1-methylpiperidine (0·08M), and (E) trimethylamine (0·08M), all in benzene.

fell in the order Me_3N, $Me{\cdot}C_5H_{10}N$, $(n\text{-}C_3H_7)_3N$, and $(Ph{\cdot}CH_2)_3N$, corresponding to inhibition of association by the increasing bulk of the substituents. Like the stronger absorptions given by dialkylanilines, those from trialkylamines did not obey Beer's dilution law. Addition of more trialkylamine (all of those studied are virtually transparent in the 4500—6000 Å region) led to an increase in the level of absorption in line with the suggested reversible association. The interaction of quinones and triethylenediamine, $N[{\cdot}CH_2{\cdot}CH_2{\cdot}]_3N$, was examined as the nitrogen atoms in this type of amine are much less hindered than that in trimethylamine.[10] Compared with the latter amine, triethylenediamine gave more strongly absorbing solutions (too strong to include in the Figure), the position of $\lambda_{max.}$ for the complex approaching those given by dimethylaniline (Table).

In suggesting that the oxidation–reduction step takes place within a molecular complex it must be remembered that the other condition of a suitable redox potential must be fulfilled before ready reaction will take place. Thus dimethylaniline is not appreciably oxidised by chloranil at room temperature in dilute solution in the dark, in spite of the obvious presence of a large concentration of complex. Similarly 2 : 5-dichloro-3 : 6-dimethoxy-*p*-benzoquinone gives an immediate brown colour with triethylamine but no dehydrogenation takes place in the dark (see below) as the oxidation potential of this quinone must be considerably lower than that of chloranil.

More detailed discussion of redox potentials is hampered by the lack of knowledge of the nature of the rate-determining hydrogen-transfer step in the amine–quinone reactions;

[9] Foster, Hammick, and Parsons, *J.*, 1956, 555.
[10] Cf. Brown, *J.*, 1956, 1248.

and the possibility that different pairs of components may react by different mechanisms must also be kept in mind.

The oxidation potentials of halogenated *p*-benzoquinones have only been determined for the overall two-electron reaction: $Q + 2e + 2H^+ \longrightarrow QH_2$. The fact that quinones with highest potentials [11] on this scale are also the most generally effective in dehydrogenating olefins and amines does not prove that a hydride-transfer mechanism is necessarily operating,* as the (unknown) potentials for single-electron steps (*e.g.*, acceptance of a hydrogen atom by the quinone) may run in a similar order. As mentioned above, a quinone, such as iodanil, which does not readily form complexes may not oxidise an amine despite its apparently suitable high potential.

For the amine component it seems that complex formation with quinones and the susceptibility of an $\rangle N{\cdot}CH\langle$ grouping towards oxidation are often in opposition. Thus triethylamine is oxidised more readily than trimethylamine, although for steric reasons the latter is likely to form a higher concentration of complex. Also, the slow oxidation of substituted benzylamines may be due to poor association for steric reasons (Figure), and not because of any particular difficulty in attack of a C–H bond in the $N{\cdot}CH_2Ar$ grouping. On the other hand, it is probable that the reduction potential and complex-forming power of dihydro-1-*p*-methoxyphenylpyridine (VI) act together to give the very rapid reaction observed with chloranil.

The tertiary-amine–quinone reactions discussed above were carried out in the dark, or in subdued light if the reaction was fast. Some reactions which did not proceed under these conditions were promoted by daylight: this may be attributed to photochemical activation of the molecular complex. Thus 2 : 5-dichloro-3 : 6-dimethoxy-*p*-benzoquinone and triethylamine gave a reddish-brown solution in benzene which slowly became blue on exposure to light. Similarly 1-methylpiperidine and chloranil gave a blue colour owing to dehydrogenation of the ring, a reaction which did not take place in the dark. The " dark reaction " in which the ethyl group of 1-ethylpiperidine is selectively dehydrogenated shows that attack on the annular α-CH group is relatively difficult in the absence of light; this could be rationalised in terms of a homolytic or a heterolytic mechanism, no decision being possible at present.

This paper has been confined to the reactions of *p*-benzoquinones; it may be noted that *o*-chloranil reacts readily with trialkylamines [13] but the products have not yet been determined.

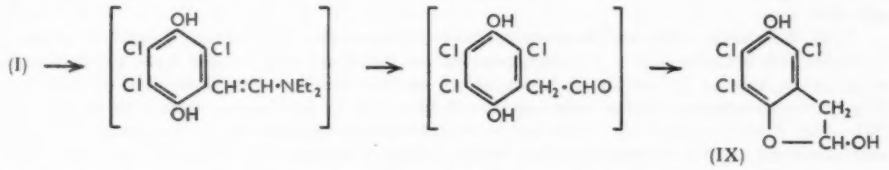
Molecular Complex Formation in the Indole Series.—The production of a blue colour from chloranil and 1-methylindole in ether has been reported.[14] Pure 1-methylindole [15] (kindly supplied by Dr. G. F. Smith) immediately gave a magenta colour in ether and a dull violet colour in benzene, neither colour changing on storage. It seems probable that the earlier workers used an impure amine. Two groups of workers [16,17] have observed that the dehydrogenation of 2 : 3-*cyclo*alkylindoles proceeds better with chloranil than by other methods. Clearly such reactions may be assisted by molecular-complex formation between the quinone and the substituted indoles.

Properties of the Dialkylaminovinylquinones.—The quinonoid structure for the blue compound (I) was indicated by its ease of reduction to colourless products and by its infrared absorption, carbonyl peaks appearing near 1670 and 1640 cm.$^{-1}$. The latter band is relatively weak and this, together with its low frequency, suggests that it arises from the

* A hydride-transfer mechanism has been favoured for olefin–quinone reactions.[12]

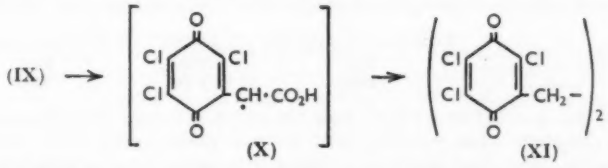
[11] Values given in this paper are for solutions of the quinones in benzene (Kvalnes, *J. Amer. Chem. Soc.*, 1934, **56**, 667).
[12] Braude, Jackman, and Linstead, *J.*, 1954, 3548.
[13] Horner and Spietschka, *Annalen*, 1955, **591**, 1.
[14] Ciusa and Ciamician, *Gazzetta*, 1909, **41** 667.
[15] Cf. Potts and Saxton, *J.*, 1954, 3548.
[16] Treibs, Steinert, and Kirchof, *Annalen*, 1953, **581**, 54.
[17] Barclay and Campbell, *J.*, 1945, 530.

carbonyl group conjugated with the electron-donating side-chain. The other band (at 1670 cm.$^{-1}$) has the normal quinone position and intensity and represents the non-conjugated carbonyl function.

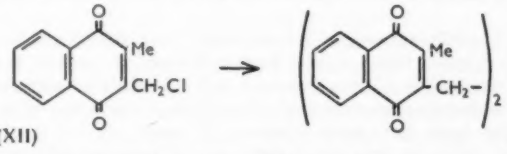


Catalytic hydrogenation (2 mols. of hydrogen) of the blue quinone (I) gave a colourless solution, but the product was difficult to purify. The blue colour of the quinone was also rapidly discharged by aqueous sodium dithionite and a crystalline compound free from nitrogen was isolated. The lactol structure (IX) is proposed for this on the basis of analytical data and infrared and ultraviolet absorption, the last resembling closely that of an alkyltrichloroquinol. Its formation may take place as indicated, hydrolysis of the enamine group occurring readily after the quinone-carbonyl system has been reduced.

Oxidation of the lactol with chromic acid in acetone gave a yellow, high-melting compound, $(C_7H_2O_2Cl_3)_n$, obviously a quinone. The low solubility of this compound (rendering molecular-weight determination by solution techniques difficult) indicated that it was not a simple alkyltrichloroquinone. The infrared absorption in the C–H bending region suggested that only methylene groups were present, and the compound is therefore formulated as (XI). This compound could arise by dimerisation of an intermediate radical, *e.g.*, (X), decarboxylation occurring at some stage ($\beta\gamma$-unsaturated acids). Stabilisation of radicals (and so dimerisation) by groups containing a carbonyl function has been encountered previously, notably in the formation of succinic acids by dimerisation of radicals.[18] Somewhat similar reactions to those in which the quinone (XI) is formed appear to be involved in the preparation of the quinone (XIII) by successive hydrogenation and oxidation of the chloromethyl compound (XII).[19]



A solution of the blue quinone (I) in benzene was unaffected when shaken with dilute aqueous acids, but the colour of an acidified methanol solution was slowly discharged; the expected hydrolysis product containing an aldehydic grouping proved difficult to purify.



This blue quinone was very reactive towards dilute alkaline reagents, but the reactions are undoubtedly caused by replacement of chlorine *para* to the unsaturated side-chain (see following paper) as the naphthaquinone compound (IV) was relatively stable.

[18] Kharasch and Gladstone, *J. Amer. Chem. Soc.*, 1943, **65**, 15; Kharasch, Jensen, and Urry, *J. Org. Chem.*, 1945, **10**, 386.
[19] Thomson, *J.*, 1953, 1190.

Experimental

M. p.s were determined on a Kofler hot stage. Alumina deactivated with dilute acetic acid [20] was generally used for chromatography of the quinones. Light petroleum had b. p. 40—60°.

2 : 3 : 5-*Trichloro*-6-2′-*diethylaminovinyl*-p-*benzoquinone* (I).—A solution of chloranil (0·99 g.) in redistilled benzene (160 c.c., deoxygenated by nitrogen) was treated with triethylamine (1 g.), then kept at 20° in the dark for 24 hr. under nitrogen. The deep blue solution was filtered, to give triethylamine hydrochloride (0·33 g.), m. p. and mixed m. p. in a sealed tube 253—254° (from propan-2-ol). One half of the filtrate was concentrated under reduced pressure and adsorbed on deactivated alumina (80 g.). Rapid elution with benzene gave the *vinylquinone* (0·21 g.), m. p. 127—131° (raised to 131—132° on crystallisation from benzene–light petroleum) (Found: C, 46·8; H, 3·85; N, 4·35; Cl, 34·45. $C_{12}H_{12}O_2NCl_3$ requires C, 46·7; H, 3·9; N, 4·55; Cl, 34·45%). The second half was extracted with 5% sodium hydroxide solution (150 c.c.), dried, and evaporated under reduced pressure to give the vinyl-quinone (0·153 g.), m. p. 125—129°, raised to 131—132° on crystallisation. Acidification of the alkaline extract and extraction with ether gave a brown solid (0·33 g.) which on sublimation *in vacuo* gave impure tetrachloroquinol (0·2 g.), m. p. 210—214°, raised to 226—230° by crystallisation from benzene. Acetylation afforded the diacetate, m. p. and mixed m. p. 252—253° (from benzene).

The molecular weight of the blue quinone, determined in benzene solution by isothermal distillation, was 350 (calc., 308); the somewhat high value is probably due to partial decomposition during the several days necessary for the attainment of equilibrium.

Reduction of the Diethylaminovinylquinone (I).—The quinone (0·6 g.) in " AnalaR " ethyl acetate (250 c.c.) was shaken with hydrogen in the presence of pre-reduced Adams catalyst (0·1 g.). Absorption was rapid until 110 c.c. had been taken up (calc. for $2H_2$: 100 c.c.). The resulting pale yellow solution became blue on exposure to air. Evaporation of the filtered solution under nitrogen gave an impure white solid (0·62 g.), m. p. 155—160°, which decomposed on attempted crystallisation.

Solutions of the quinone (1 g.) in acetone (150 c.c.) and sodium dithionite (10 g.) in water (200 c.c.) were mixed under nitrogen. When the mixture became colourless, water and ether were added. The product from the dried ethereal layer was crystallised from water, to give material (0·45 g.), m. p. 162—167°. The pure *lactol* (IX) had m. p. 166—167° (from benzene) (Found: C, 37·85; H, 1·95; Cl, 41·4. $C_6H_5O_3Cl_3$ requires C, 37·6; H, 2·0; Cl, 41·6%). The compound showed infrared hydroxyl absorption. Ultraviolet absorptions (in EtOH) were:

	Trichloro-*p*-toluquinol	Lactol	Tetrachloro-*p*-quinol
$\lambda_{max.}$ (Å)	3020	3060	3090
$\varepsilon_{max.}$	4800	5100	9300

A solution of the lactol (0·28 g.) in acetone (20 c.c.) was treated with 8N-chromic acid until oxidation was complete. The product (0·22 g.) was isolated with ether and adsorbed on deactivated alumina (20 g.) from benzene. Elution with benzene gave the *quinone* (XI) (0·15 g.), m. p. 268—273° (raised to 275—276° on crystallisation from benzene–acetone) (Found: C, 37·2; H, 0·95; Cl, 47·45. $C_{14}H_4O_4Cl_6$ requires C, 37·45; H, 0·9; Cl, 47·4%), having (in perfluorocarbon) carbonyl peaks at 1687 and 1670 cm.$^{-1}$ and a methylene peak at 1456 cm.$^{-1}$, and (in dioxan) $\lambda_{max.}$ 2815 Å (ε 26,300). The related trichloro-*p*-toluquinone had (in dioxan) $\lambda_{max.}$ 2800 Å (ε 16,500).

2 : 3 : 5-*Tribromo*-6-2′-*diethylaminovinyl*-p-*benzoquinone*.—A solution of bromanil (2·0 g.) and triethylamine (3·5 g.) in benzene (400 c.c.) was kept at 20° under nitrogen in the dark for 24 hr. Triethylamine hydrobromide (0·6 g.) was removed and the solution evaporated. The residue was chromatographed in benzene on deactivated alumina, to give the blue *quinone* (0·47 g.), m. p. 114—116° (from light petroleum–benzene) (Found: C, 32·6; H, 2·9; N, 3·45. $C_{12}H_{12}O_2NBr_3$ requires C, 32·7; H, 2·75; N, 3·15%), $\lambda_{max.}$ (in dioxan) 3210 and 6450 Å (ε 28,900 and 8800 respectively).

Triethylamine and Other Quinones.—*p*-Benzoquinone, 2 : 5-dichloro-3 : 6-dimethoxy- and 2 : 6-dichloro-3 : 5-dimethoxy-*p*-benzoquinone were recovered in about 90% yields from attempted reactions with triethylamine in benzene, as described for chloranil. No blue colours were formed.

[20] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.

2 : 6-*Dichloro*-3-2′-*diethylaminovinyl*-p-*benzoquinone*.—A solution of 2 : 6-dichloro-*p*-benzoquinone (2·6 g.) and triethylamine (5 g.) in benzene (100 c.c.) was heated under reflux for 20 min. Filtration of the cooled solution removed dark insoluble material (2 g.). The filtrate was evaporated under reduced pressure and adsorbed on deactivated alumina (50 g.). Rapid elution with benzene followed by crystallisation of the product from ligroin gave the blue *quinone* (0·25 g.), m. p. 97—99° raised to 100—102° on recrystallisation (Found: C, 52·2; H, 4·8; N, 5·05; Cl, 25·55. $C_{12}H_{13}O_2NCl_2$ requires C, 52·6; H, 4·8; N, 5·1; Cl, 25·85%).

In a similar experiment with the quinone (0·71 g.) and triethylamine (0·81 g.) in benzene (80 c.c.) under nitrogen at 20° for 24 hr. in the dark, triethylamine hydrochloride (0·13 g.) and the blue quinone (25 mg.), m. p. 100—101°, were obtained.

2 : 5-*Dichloro*-3-2′-*diethylaminovinyl*-p-*benzoquinone*.—A solution of 2 : 5-dichloro-*p*-benzoquinone (3 g.) and triethylamine (6 g.) in benzene (100 c.c.) was heated under reflux for 1 hr. The solution was filtered to remove black material (3·5 g.), and evaporated under reduced pressure to give a product which, in benzene, was adsorbed on deactivated alumina (50 g.). Rapid elution with benzene and crystallisation from ligroin yielded the blue quinone (0·26 g.), m. p. 88—95°. Recrystallisation gave the pure *quinone*, m. p. 96—98° (decomp.) (Found: C, 53·05; H, 4·8; N, 5·45; Cl, 24·85%).

2-*Chloro*-3-2′-*diethylaminovinylnaphtha*-1 : 4-*quinone* (IV).—A solution of 2 : 3-dichloronaphtha-1 : 4-quinone (6 g.) and triethylamine (9 g.) in benzene (300 c.c.) was heated under reflux for 72 hr. The amine hydrochloride (0·3 g.) was filtered off and the filtrate evaporated under reduced pressure. The product was chromatographed on deactivated alumina (130 g.). Elution with benzene–light petroleum (1 : 3) yielded unchanged quinone (5·1 g.). Elution with benzene–light petroleum (1 : 1) gave red material (15 mg.). Elution with benzene gave the *vinyl-quinone* (0·2 g.), m. p. 91—95° (raised to 93—95° by recrystallisation from light petroleum, b. p. 40—60°) (Found: C, 66·2; H, 5·6; N, 4·45. $C_{16}H_{16}O_2NCl$ requires C, 66·3; H, 5·55; N, 4·85%). The quinone in ethyl acetate in the presence of Adams catalyst absorbed 2 mols. of hydrogen. A similar yield of the vinyl-quinone was obtained on reaction of 2-chloronaphtha-1 : 4-quinone and triethylamine in boiling benzene.

2 : 3 : 5-*Trichloro*-6-*piperidinovinyl*-p-*benzoquinone* (V).—A solution of 1-ethylpiperidine (1·13 g.) and chloranil (1·23 g.) in benzene (150 c.c.) was kept in the dark under nitrogen at 20° for 24 hr. The blue solution was washed with N-sodium hydroxide, then evaporated under reduced pressure to give the crude product (0·35 g.). This in benzene was filtered through deactivated alumina (20 g.). Crystallisation from aqueous acetone gave the *vinyl-quinone* (0·20 g.) as needles, m. p. 145—146° (decomp.) (Found: C, 48·5; H, 4·1. $C_{13}H_{12}O_2NCl_3$ requires C, 48·7; H, 3·8%).

General Properties of Dialkylaminovinylquinones.—The benzoquinone compounds decomposed to brown materials on melting, and their m. p.s depended on the rate of heating. The blue colour was rapidly discharged by alkaline reagents in homogeneous solution. Deactivated, neutral alumina was necessary for chromatography but appreciable losses occurred unless elution was rapid. The colour of a blue solution in methanol faded slowly on the addition of N-sulphuric acid. The naphthaquinone (IV) was more stable thermally and towards alkaline reagents.

Reaction of Chloranil with Dihydro-1-p-*methoxyphenylpyridine* (VI).—The amine (0·125 g.) in benzene (5 c.c.) was added to chloranil (0·165 g.) in benzene (10 c.c.), a green precipitate immediately being formed. After 30 min. the salt (cf. VII) (0·274 g., 95%) was collected. A thoroughly dried sample had m. p. 111—114° (dependent on rate of heating) (Found: C, 47·6, 47·5; H, 2·7, 2·85; N, 3·5, 3·5; Cl, 35·6, 35·4. Calc. for $C_{18}H_{13}O_2NCl_4$: C, 49·9; H, 3·0; N, 3·25; Cl, 32·8%). It was thought that the low carbon and the high chlorine analyses might be due to coprecipitation of chloranil, but repetition of the experiment with a deficiency (0·85 equiv.) of chloranil gave material with almost the same analysis (second set of figures above). The infrared spectrum of the salt (in Nujol) indicated that no appreciable amount of chloranil or of tetrachloroquinol could be present. The green salt (0·146 g.) was shaken with dilute hydrochloric acid and ether. The ether extract gave a solid (82·4 mg., theor. 83·5 mg.) which on crystallisation from benzene–light petroleum afforded tetrachloroquinol (50 mg.), m. p. and mixed m. p. 233—234°, whose infrared spectrum was identical with that of authentic material. The aqueous solution was evaporated to give a solid (75·2 mg., theor. 74·6 mg.) which on crystallisation from propan-2-ol–*iso*propyl ether gave 1-*p*-methoxyphenylpyridinium chloride (49·2 mg.) (infrared spectrum identical with that of authentic material).

Dehydrogenation of iso*Butyldimethylamine.*—A solution of the amine (0·404 g.) and chloranil (0·492 g.) in pure peroxide-free dioxan (10 c.c.) was kept under nitrogen in the dark at 20° for 24 hr. The solution was then purple and a small precipitate of amine hydrochloride had been formed. The whole was acidified with dilute sulphuric acid and filtered and the filtrate treated with 2 : 4-dinitrophenylhydrazine reagent. The derivative was extracted with benzene and chromatographed on kieselguhr–bentonite. Chloroform eluted *iso*butyraldehyde 2 : 4-dinitrophenylhydrazone (55 mg., 22% based on chloranil), m. p. 183—188°. Crystallisation from propan-2-ol gave the pure compound as orange needles, m. p. and mixed m. p. 187—188°.

In a similar experiment with benzene (50 c.c.) as solvent, 48% of chloranil was recovered.

Reactions of Chloranil with Other Amines.—The following experiments were carried out under nitrogen in the dark at 20° for 24 hr. None of the amines gave blue quinones.

Trimethylamine. The amine (0·118 g.) and chloranil (0·246 g.) in benzene (25 c.c.) gave a reddish-brown solution. After 24 hr. the solution had become purple and some amine hydrochloride had separated. Chloranil (0·134 g., 55%) was recovered. From absorption measurements the yield of 2 : 3 : 5-trichloro-6-dimethylaminobenzoquinone was estimated to be 4% (based on initial chloranil). This *quinone*, isolated from a larger-scale experiment, had m. p. 120—122° [from light petroleum (b. p. 60—80°)] (Found: C, 38·25; H, 2·4; N, 5·6. $C_8H_6O_2NCl_3$ requires C, 37·75; H, 2·4; N, 5·5%); for its ultraviolet absorption see the following paper. Whether the formation of the dimethylaminoquinone depends on the presence of traces of water has yet to be determined.

*Dimethyl*iso*propylamine.* A brownish colour was formed immediately on adding the amine (0·174 g.) to chloranil (0·246 g.) in benzene (25 c.c.). After 24 hr. the solution had become greenish-brown and some amine hydrochloride had separated. Chloranil (0·125 g., 51%) was recovered.

Tetramethylethylenediamine. A deep red-brown colour was formed on adding the amine (0·464 g.) to chloranil (0·492 g.) in benzene (60 c.c.), and a dark precipitate began to separate after 10 min. After 24 hr. the precipitate (mixture of amine hydrochloride and black material, m. p. >350°) was collected and chloranil (31 mg., 6%) was isolated from the filtrate.

Tetramethylmethylenediamine. A solution of the amine (0·204 g.) and chloranil (0·492 g.) in benzene (100 c.c.) was kept at 26°. After various times, 10 c.c. portions were withdrawn and washed with 0·04N-hydrochloric acid and water. The combined washings were adjusted to pH 5—6 and treated with dimedone [12 c.c. of a 0·04M-solution in methanol–water (1 : 19)] at 90° for 10 min. and then kept at 20° for 24 hr. The yield of formaldehyde derivative is a measure of attack on the central methylene group:

Time (hr.)	1	2·5	4	24	48	120
Formaldehyde dimethone (%)	99	83	72	62	57	36

Benzyldimethylamine. A solution of chloranil (0·492 g.) and the amine (0·27 g.) in benzene (50 c.c.) was heated under reflux for 24 hr. in nitrogen which thence passed into dimedone solution (no formaldehyde derivative was precipitated). The purple solution was filtered from dark brown material containing some amine hydrochloride and divided in halves. One portion was treated with an excess of 2 : 4-dinitrophenylhydrazine reagent, to give benzaldehyde derivative (26%). The other portion was washed with dilute hydrochloric acid and chromatographed on deactivated alumina, chloranil (50%; contaminated with some purple 2 : 3 : 5-trichloro-6-dialkylaminoquinone) being recovered.

Tribenzylamine. A solution of the amine (0·576 g.) and chloranil (0·492 g.) in benzene (40 c.c.) was heated under reflux, the yield of benzaldehyde (as its 2 : 4-dinitrophenylhydrazone) being estimated at different times:

Time (hr.)	18	28	72	98	120
Ph·CHO deriv. (%)	18	30	45	53	60

Reactions of Triethylamine with Other Chloroquinones.—A solution of the amine (4·04 g.) and 2 : 3-dichlorobenzoquinone (3·54 g.) in benzene (100 c.c.) was kept under nitrogen in the dark for 24 hr. A black precipitate (4·6 g.) which separated was washed with water to remove amine hydrochloride (1·77 g.). The black solid (insoluble in the common organic solvents), m. p. >320°, was dried *in vacuo* at 50° (Found: C, 49·0; H, 3·4; N, 2·0; Cl, 24·9%). Apart from analytical differences this material was not the quinhydrone (from the original quinone and the related quinol) which had m. p. 100—104°. No crystalline compounds were obtained from the benzene solution.

XUM

A similar reaction with chloro-*p*-benzoquinone (2·89 g.) gave a black precipitate (3·85 g.), and unchanged quinone (0·34 g.) was recovered from the benzene solution. Amine hydrochloride (0·69 g.) was removed by aqueous extraction of the black solid, leaving material, m. p. >320°, which was dried *in vacuo* at 50° (Found: C, 54·55; H, 2·5; N, 1·3; Cl, 16·25%).

The analyses of these black products did not fit with any simple compositions, but indicated that the products were formed from several molecules of quinone per molecule of amine, with loss of some hydrogen chloride.

Reaction of Triethylamine with p-*Benzoquinone.*—A solution of the amine (0·404 g.) and quinone (0·216 g.) in benzene (25 c.c.) was kept under nitrogen in the dark at 20° for 24 hr. The pale orange solution was evaporated to give unchanged quinone (0·190 g., 88%; almost certainly low owing to some loss of the volatile compound).

The amine (1·01 g.) and quinone (1·08 g.) in benzene (25 c.c.) were heated under reflux for 4·5 hr. with the exclusion of light. Filtration of the cooled mixture gave black solid and a red solution. The solid, washed with warm benzene and warm water and dried (0·69 g.), had m. p. > 320° [Found: C, 63·85; H, 5·4; N, 2·5. $(C_{30}H_{31}O_{10}N)_n$ requires C, 63·7; H, 5·55; N, 2·5%].

The authors thank Professors E. R. H. Jones, G. Gee, and D. H. Hey for encouragement of the work described in this and the following papers. They also thank Dr. G. D. Meakins for the determination of spectra and Mr. E. S. Morton for microanalyses. Financial assistance from the University of Manchester (to S. D.) and from the Department of Scientific and Industrial Research (to D. B.) is gratefully acknowledged.

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982. *Syntheses of Substituted Amino-, Aminovinyl-, and Aminobutadienyl-*p-*quinones.*

By D. BUCKLEY, H. B. HENBEST, and P. SLADE.

Dialkylaminovinylquinones can often be synthesised in good yield from halogenated quinones, acetaldehyde, and secondary amines, isolation of the enamines being unnecessary. A dialkylaminobutadienyl-quinone has been prepared in the naphthalene series, by using 1-diethylaminobutadiene or, less efficiently, a mixture of diethylamine and crotonaldehyde. Replacement of chlorine in the blue dialkylaminovinyltrichlorobenzoquinones can lead to purple or green compounds. For comparison, some reactions between quinones and primary and secondary amines have been carried out. The light absorption properties of these coloured compounds are discussed; it is considered that the side-chains, $(CH{=}CH)_{1-2}{\cdot}NR_2$, in the new quinones are of *trans*-geometry.

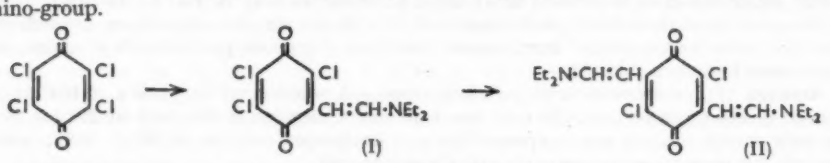
IN the preceding paper,[1] the formation of coloured dialkylaminovinyl-quinones from quinones and simple tertiary amines containing *N*-ethyl groups was recorded. The second stage of these reactions was considered to be the condensation of an enamine ($R_2N{\cdot}CH{:}CH_2$) with the starting quinone; it is with the further study of this coupling reaction that the present paper is concerned.

Though the original intention was to prepare diethylvinylamine * from diethylamine and acetaldehyde and condense it with chloranil, it was found that the deep blue colour of the diethylaminovinyl-quinone (I) was rapidly produced on successively adding the aldehyde and the secondary amine to a solution of the quinone, and preparation of the (probably unstable) enamine was not therefore necessary. The reaction between chloranil, diethylamine, and acetaldehyde (molar ratios 1 : 2 : 1) in benzene at room temperature was complete within 10 minutes, and the blue quinone (I) (identical with that previously

* Its preparation by another method has been claimed by Meyer and Hopff.[2]

[1] Buckley, Dunstan, and Henbest, preceding paper.
[2] Meyer and Hopff, *Ber.*, 1921, **54**, 2274.

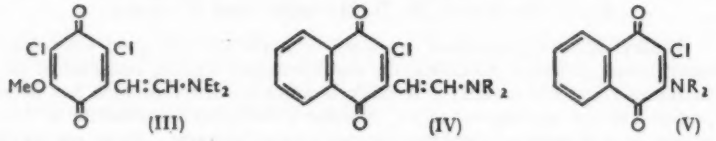
obtained from triethylamine) was readily isolated in 80% yield. The speed of formation and condensation of the enamine is therefore greater than that of reaction between the quinone and the secondary amine, leading to the replacement of chlorine by a diethylamino-group.



With further amounts of acetaldehyde and diethylamine the blue quinone (I) was converted into the purple bisdiethylaminovinyl-quinone (II); the *p*-orientation of the new substituents is suggested by analogy with the reactions of chloranil and related quinones with other nucleophilic reagents (cf. below).

Blue compounds related to the quinone (I) have been obtained also from dimethylamine, morpholine, pyrrolidine, piperidine, hexamethyleneimine, diethanolamine, and methylaniline.

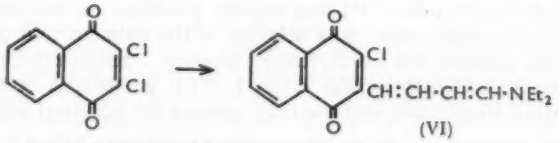
As a rule those quinones which react with a primary amine also react with a mixture of acetaldehyde and diethylamine to give diethylaminovinyl-quinones. Thus, in keeping with the reaction with *n*-butylamine (below), a methoxyl group is replaced from 2 : 6-dichloro-3 : 5-dimethoxybenzoquinone, and the blue quinone (III) is produced. 2 : 3-Dichloronaphthaquinone, acetaldehyde, and diethylamine gave the purple compound (IV; R = Et) (94%), previously obtained in low yield from triethylamine. The nitrogen atom in dimethylamine is less shielded than that in diethylamine, so in this reaction the former amine gave also an appreciable amount of the red dimethylamino-quinone (V; R = Me) and less (35%) of the dimethylaminovinyl compound (IV; R = Me).



Qualitative tests with acetaldehyde and diethylamine showed that many other quinones formed purple–blue solutions. *p*-Benzoquinone gave a purple solution but the product was hard to purify.

Tests with diethylamine and chloranil showed that aldehydes, $R{\cdot}CH_2{\cdot}CHO$, usually gave blue solutions, but the colours were weaker and the blue compounds more reactive and difficult to isolate by conventional techniques. The results described in this and the following paper show that the ease of the coupling reaction decreases in the order, $CH_2{:}CH{\cdot}NR_2$, *cis*-$CH{:}CH{\cdot}NR_2$, *trans*-$CH{:}CH{\cdot}NR_2$. These aldehydes and secondary amines would be expected to generate largely or wholly *trans*-enamines (cf. infrared evidence below).

The synthesis probably cannot be extended to ketones, as the attempted reaction of acetone with chloranil and morpholine led only to replacement of chlorine by morpholine residues.



A compound with a more extended chromophore was also prepared. 2 : 3-Dichloronaphthaquinone, crotonaldehyde, and diethylamine gave 20% of the blue compound (VI),

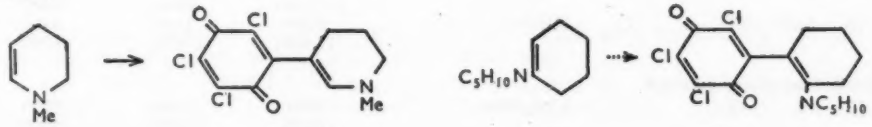
with a larger amount of the product formed by replacement of one chlorine by a diethylamino-residue. The presumed intermediate, CH_2:CH·CH:CH·NEt_2, can be readily prepared,[3] and gave the same blue compound (VI) in 80% yield in 3 min. at room temperature. It is possible that the reactions are assisted by complex formation between the quinone and the unsaturated amine (cf. preceding paper).

In general, the reactions between chloro-quinones, acetaldehyde, and secondary amines were rapid, often being complete in less than 10 minutes at room temperature. Since dehydration is involved in the formation of the enamine, it is noteworthy that the blue quinone was formed also in aqueous dioxan.

Configuration of the Side-chain, and Infrared Absorption of the New Quinones.—The methods used to give the quinones with $(CH{:}CH)_{1-2}{\cdot}NR_2$ side-chains would be expected to afford the more extended, and probably more stable, *trans*-compounds, and the following observations support this assignment.

The enamine (VII) generated by dehydrogenation of 1-methylpiperidine (following paper) yields a blue quinone (VIII), in which the chromophoric substituents must be *trans* in the side-chain. Apart from expected minor differences, the ultraviolet absorption of the quinone (VIII) was similar to that of related compounds with a $CH{:}CH{\cdot}NR_2$ substituent. In contrast, the reaction between the enamine (IX) and chloranil, which in theory could give a compound with a *cis*-chromophoric group (*i.e.*, X), gave a colourless solution: this reaction is being further studied, but there is no evidence that the quinone (X) is formed.

Each of the quinones containing a $CH{:}CH{\cdot}NR_2$ substituent exhibited an infrared band near 960 cm.$^{-1}$. That this is due to a *trans*-double bond is supported by the fact that the butadienyl-quinone (VI) and the bisdialkylaminovinyl-quinone (II) gave absorption bands at 963 and 958 cm.$^{-1}$ respectively, of approximately double the intensity. (The simpler enamine, $[CH_2]_5 > N{\cdot}CH{:}CHEt$, prepared from piperidine and *n*-butyraldehyde,[4] exhibited a band of medium strength at 940 cm.$^{-1}$, consistent with the presence of a *trans*-double bond.)



(VII) (VIII) (IX) (X)

Quinones with an unsaturated amine side-chain, *e.g.*, (I), (IV), and (VI), gave two carbonyl bands, one of normal intensity and position (~1670 cm.$^{-1}$) for a quinone and the other of lower intensity and frequency (~1640 cm.$^{-1}$). The latter probably represents the carbonyl group conjugated with the unsaturated side-chain.

Some Reactions of Dialkylaminovinylquinones with Nucleophiles.—Owing to the presence of chlorine *para* to the unsaturated side-chain, blue quinones such as (I) react readily with nucleophilic reagents such as amines or dilute alkali. Thus, the disubstituted quinone (II) was formed from (I) with an excess of acetaldehyde and the secondary amine, whereas the naphthaquinone (IV) was not substituted further under the same conditions.

Reactions of the blue quinone (XI) with a primary (*n*-butylamine) and a secondary amine (dimethylamine) proceeded differently. An excess of the latter amine led to the quinone (XII) by replacement of the *p*-chlorine atom. Reaction with *n*-butylamine was also rapid, both a chlorine and the morpholine residue being replaced by butylamino-groups, so the compound is formulated as (XIII).

Under the same conditions, secondary amine residues in the side-chains of the quinones (IV), (VI), and (XII) were not displaced by *n*-butylamine, so the unusual step in the

[3] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.
[4] Mannich and Davidsen, *Ber.*, 1936, **69**, 2106.

TABLE 1. *Absorption maxima* (Å, *with* ε *in parentheses*) *of* p-*benzoquinones in pure dioxan at* 2200—8000 Å.

No.	Subst. at position 2	3	5	6	Band I	Band II	Band III
Dimethoxy- and diamino-quinones							
1	H	MeO	H	MeO	—	2770 (17,300)	3600 (320)
2	Cl	MeO	Cl	MeO	—	3000 (13,300)	4040 (360)
3	MeO	H	H	MeO	—	2850 (17,200)	3670 (760)
4	MeO	Cl	Cl	MeO	—	2960 (12,300)	4050 (380)
5	H	NHBu	H	NHBu	—	3310; 3420 (30,600; 31,800)	4760 (270)
6	Cl	NHBu	H	NHBu	—	3480 (31,400)	4980 (300)
7	Cl	NHBu	Cl	NHBu	2240 (18,200)	3550 (25,300)	5200 (230)
8	MeO	NHBu	H	NHBu	—	3490 (22,000)	5380 (300)
9	MeO	NHBu	Cl	NHBu	2250 (21,300)	3570 (25,600)	5480 (270)
10	H	NMe_2	H	NMe_2	2220 (25,200)	3620 (22,500)	4950 (410)
11	Cl	NMe_2	Cl	NMe_2	2380 (15,900)	4140 (10,100)	—
12	H	OC_4H_8N	H	OC_4H_8N	2260 (24,600)	3680 (18,400)	5010 (570)
13	Cl	OC_4H_8N	Cl	OC_4H_8N	2410 (17,700)	4350 (11,200)	—
Amino-quinones							
14	Cl	Cl	Cl	NMe_2	2440 (14,400)	3050, 3110 (5800)	5450 (2300)
15	Cl	Cl	Cl	OC_4H_8N	2460 (15,100)	3190 (4800)	5450 (2900)
16	MeO	Cl	Cl	NHBu	2260 (17,400)	3140 (8950)	5150 (1500)
Dialkylaminovinyl-quinones							
17	Cl	Cl	Cl	$C_2H_2{\cdot}NMe_2$	2420 (7500)	3140 (29,300)	6300 (8500)
18	Cl	Cl	Cl	$C_2H_2{\cdot}NEt_2$	2410 (9700)	3160 (30,500)	6450 (8800)
19	Cl	Cl	Cl	$C_2H_2{\cdot}N<[CH_2]_4$	2430 (6700)	3160 (27,500)	6600 (8200)
20	Cl	Cl	Cl	$C_2H_2{\cdot}N<[CH_2]_5$	2420 (7800)	3160 (32,000)	6420 (9200)
21	Cl	Cl	Cl	$C_2H_2{\cdot}N<[CH_2]_6$	2400 (7500)	3180 (28,300)	6450 (8400)
22	Cl	Cl	Cl	$C_2H_2{\cdot}NMePh$	2470 (8850)	3240 (28,500)	6350 (10,300)
23	Cl	Cl	Cl	$C_2H_2{\cdot}NC_4H_8O$	2430 (5560)	3150 (22,100)	6300 (6700)
24	Cl	Cl	Cl	1 : 4 : 5 : 6-Tetrahydro-1-methylpyridyl	2570 (9300)	3250 (16,700)	7050 (8000)

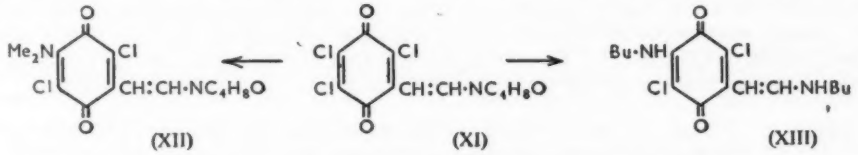
Position:	2	3	5	6	Band: I	II	II A	III
25	MeO	Cl	Cl	$C_2H_2{\cdot}NEt_2$	—	3150 (26,600)	—	6350 (7000)
26	Cl	MeO	Cl	$C_2H_2{\cdot}NEt_2$	—	3110 (26,300)	3720 (6400)	6300 (9100)
27	Cl	NHBu	Cl	$C_2H_2{\cdot}NHBu$	2260 (8550)	2960 (18,500)	4320 (25,000)	6200 (5100)
28	Cl	NMe_2	Cl	$C_2H_2{\cdot}NC_4H_8O$	2390 (14,100)	3060 (24,800)	4680 (21,600)	6300 (3800)
29	Cl	$C_2H_2{\cdot}NEt_2$	Cl	$C_2H_2{\cdot}NEt_2$	2410 (10,000)	3360 (30,300)	5370 (27,700)	6450 (4000)

XUM

TABLE 1. (*Continued.*)

Naphthaquinones Position	2	3	Band: I	II	III
30	Cl	NHEt	2370 (12,800)	2750 (22,100)	4660 (3000)
31	Cl	NMe_2	2470 (13,000)	2820 (14,500)	4760 (3100)
32	Cl	NEt_2	2470 (14,800)	2830 (12,800)	4940 (3100)
33	Cl	OC_4H_8N	2480 (14,200)	2820 (16,000)	4880 (4200)
34	H	OC_4H_8N	2380 (14,200)	2710 (17,400)	4440 (3450)
35	Cl	$C_2H_2 \cdot NMe_2$	2380 (10,100)	3210 (26,600)	5580 (12,200)
36	Cl	$C_2H_2 \cdot NEt_2$	2380 (10,200)	3230 (27,600)	5640 (13,300)
37	Cl	$C_4H_4 \cdot NEt_2$	2460 (16,000)	3650 (34,200)	6250 (29,900)

formation of (XIII) is due to the NHR grouping in the presumed initial product formed by replacement of *p*-chlorine. This initial product can possibly occur in an *o*-quinonoid form, whose greater reactivity results in amine replacement on the side-chain. [The high reactivity of *o*-quinones is well known. In a simple competitive reaction between *o*- and *p*-chloranils and *n*-butylamine (molar ratios 1 : 1 : 2), the *p*-quinone (89%) but no



(XII) (XI) (XIII)

o-quinone was recovered.] The quinones (XII) and (XIII) gave respectively dull green and brilliant green solutions in organic solvents (cf. below).

Light Absorption.—The solvent properties and unreactivity of purified dioxan made this a suitable medium for the determination of the ultraviolet and visible absorption of the present compounds. Most of the quinones show three bands, referred to as bands I, II, and III (see Table 1).

The general bathochromic effect of chlorine is apparent (pairs 1–2, 3–4, 5–7, 34–33). The visual effect in the last pair is the change in colour from orange to red.

Band I. Variation of the side-chain from dialkylamino- to dialkylaminovinyl or dialkylaminobutadienyl cause only small variations in the position of this band (nos. 14 and 17; 32, 36, and 37).

Band II. The position of this band is influenced by conjugation of the quinone system with electron-donating side-chains. Thus in the naphthaquinone series, $\lambda_{max.}$ rises for the substitutent order, NHEt, NEt_2, $Et_2N \cdot CH{:}CH$, $Et_2N \cdot [CH{:}CH]_2$ (nos. 30, 33, 36, 37). In the benzoquinone series the position of the band does not greatly change but the intensity may be trebled on replacement of an amine substituent (nos. 14—16) by a dialkylaminovinyl group (nos. 17—24). In 3 : 6-bisaminosubstituted benzoquinones, $\lambda_{max.}$ increases and ε decreases on progression from bisbutylamino- (nos. 5 and 7) to bisdimethylamino-compounds (nos. 10 and 11). For such alterations in the alkyl substituents, these changes are larger than expected; the absorption of the bisbutylamino-compounds may however be somewhat "abnormal" owing to hydrogen bonding to the carbonyl groups which would give larger resonance contributions from the quinoneimide form. In fact, these bisbutylamino-compounds (nos. 5—9) and the green quinone no. 27 could be formulated alternatively as (hydrogen-bonded) quinoneimides. Until further details concerning the

hydrogen positions are available, the compounds are written in the usual quinonoid forms (cf. formulæ XIII, XIV, XX, XXII, and XXIV). Steric inhibition of resonance may contribute to the lowered intensities of band II in the chlorinated compounds (nos. 11 and 13) and also to the decreasing intensity of this band in the compounds nos. 30, 31, and 32.

Band III. In many of the compounds this absorption band largely determines the colour of the quinone. Single absorption bands in the visible region cause the monoaminobenzoquinones (nos. 14—16) to be purple and the dialkylaminovinyl compounds (nos. 17—24) to be blue in solution. Band III (and also the ultraviolet band II) is at a shorter wavelength in naphthaquinones than in related benzoquinones, and the monoamino-compounds (nos. 30—32) are red, the dialkylaminovinylquinones (nos. 35 and 36) are purple, and the dialkylaminobutadienyl-quinone (no. 37) is blue.

The red to red-brown diaminobenzoquinones show either no selective visible absorption (nos. 11 and 13) or bands of relatively low intensity near 5000 Å (nos. 5—10 and 12).

The absorption maximum (band III) of dialkylaminovinyl-quinones varies in the expected manner with changes in alkyl substituents. Changes from dimethylamino to diethylamino (nos. 17 and 18), and from piperidino to pyrrolidino (nos. 19 and 20), cause $\lambda_{max.}$ to move to longer wavelengths. The compound no. 24 contains an extra *C*-alkyl group in the side-chain, and $\lambda_{max.}$ moves to 7050 Å.

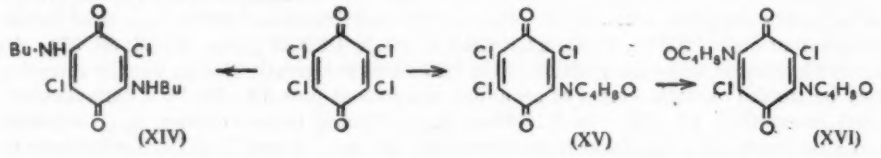
Band IIA. The compounds nos. 26—29 contain an electron-donating substituent *para* to a dialkylaminovinyl side-chain, and each shows an additional band (labelled IIA) between bands II and III (the compound no. 25 with a methoxyl group *meta* to the side-chain does not give a fourth band). In these compounds the band near 6400 Å normally responsible for a blue colour does not vary appreciably, but the position of band IIA moves to a longer wavelength and into the visible region as conjugation increases in the order MeO, NHBu, $Et_2N{\cdot}CH{:}CH$. The consequence is that the quinones nos. 27 and 28 give green solutions, and the bisdialkylaminovinyl compound no. 29 is purplish in solution.

TABLE 2. *Variation of the long-wave absorption maximum* (Å, *with* ε *in parentheses*) *of 2-chloro-3-2′-diethylaminovinylnaphthaquinone* (IV) *with solvent.*

*cyclo*Hexane	5450 (12,500)	Pyridine	5750 (13,000)
Dioxan	5640 (13,300)	Propan-2-ol	5800 (13,300)
Benzene	5700 (13,200)	Nitromethane	5850 (13,300)
Acetone	5750 (13,700)	Pyridine–water (9 : 1)	5850 (13,200)

The absorption maximum, in the visible region, of the dialkylaminovinylnaphthaquinone (IV) moves to longer wavelength in the usual way with increasing polarity of solvent (Table 2); the compounds are not sufficiently polarised to give the (reverse) effect described by Brooker, Keyes, and Heseltine.[5]

Reactions of Quinones with Primary and Secondary Amines.—Many examples of such reactions have been described previously;[6,7] the following experiments were carried out in order to supplement and amplify the present work, involving the less well-known enamines as nucleophilic reagents.



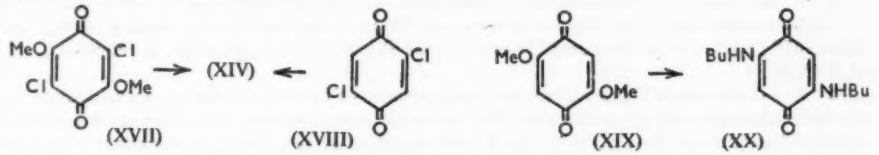
(XIV) (XV) (XVI)

The reaction of chloranil with *n*-butylamine paralleled the formation of the green quinone (XIII) from the quinone (XI) in that a disubstituted product (XIV) was obtained—even when a deficiency of amine was used. Reactions between chloranil and

[5] Brooker, Keyes, and Heseltine, *J. Amer. Chem. Soc.*, 1951, **73**, 5350.
[6] Fieser, *ibid.*, 1926, **48**, 2936.
[7] Anslow and Raistrick, *J.*, 1939, 1446.

different proportions of the secondary amine, morpholine, gave the substituted quinones (XV) and (XVI).

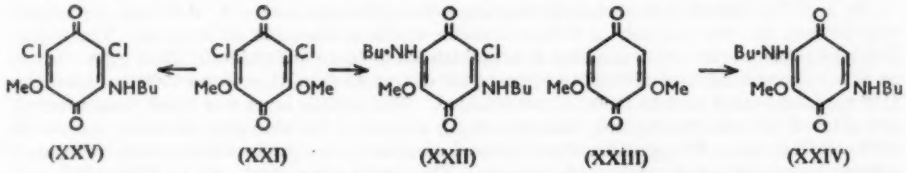
In the formation of the blue quinone (III) it was observed that methoxyl, not chlorine, was displaced by an enamine grouping (as already observed in the naphthaquinone series [6]). The reaction of the dichlorodimethoxyquinone (XVII) with the *n*-butylamine similarly gave the diamine (XIV) in high yield and the formation of chloride ion could not be detected. Quinones containing adjacent hydrogen and chlorine substituents are attacked by amines (and by enamines—see following paper) at either position. Thus the sparingly soluble quinone (XIV) was isolated in low yield after reaction of the dichloroquinone (XVIII) with *n*-butylamine, but replacement of chlorine occurred simultaneously (silver test). In these examples the replacement of methoxyl or hydrogen from positions adjacent to chlorine substituents appears to be facilitated by the electron-attracting properties of the halogen group.



Compared with the formation of the diamino-quinone (XIV) from the dichlorodimethoxyquinone (XVII) the rate of formation of the unchlorinated analogue (XX) from the dimethoxy-quinone (XIX) was very slow; this may in part be due to poorer complex association between the amine and the unchlorinated dimethoxyquinone.

The above and earlier work show that reactions of benzoquinones with an excess of primary amine commonly lead to *para*-disubstituted products. The reactions of the dimethoxy-quinones (XXI) and (XXIII) with *n*-butylamine provide further examples, the products (XXII) and (XXIV) being obtained, but more slowly.

However, the dichlorodimethoxy-quinone (XXI) differed from its isomer (XVII) in that a (purple) monosubstituted compound could be isolated when less butylamine was used. Analyses confirmed that a methoxyl group had been displaced, the product having the structure (XXV). It is not difficult to see why the monosubstituted compound (XXV) was readily obtained whereas its isomer from (XVII) was further substituted. In (XXV)



the methoxyl and butylamino-groups are in a cross-conjugated arrangement and the polarisation necessary for the second stage in the reaction is opposed by the methoxyl group. In the monosubstituted compound from (XVII) the systems MeO·C:C·C:O and Bu·NH·C:C·C:O are separated by single bonds, and mutual polarisation (leading on the methoxyl side to displacement of this group) of the systems is encouraged.

Experimental

Compounds whose light absorptions are recorded in the Tables are either described in this group of papers or were prepared by known methods.

General Procedure for the Preparation of Dialkylaminovinyl-quinones.—The secondary amine (2 mol.) was added to a stirred solution of the quinone (1 mol.) and freshly distilled acetaldehyde (1 mol.) in benzene at 20—25° in the presence of a few grams of anhydrous sodium sulphate (this was not essential but improved the yields of blue quinones). After 10 min., 0·5N-sulphuric

acid was added to extract amine salts, and the benzene layer was dried and concentrated under reduced pressure. The solution of the coloured quinone was filtered through a small amount of neutralised, deactivated alumina,[8] and the product was crystallised. More extensive chromatography on the same adsorbent was sometimes necessary.

2 : 3 : 5-*Trichloro*-6-2′-*diethylaminovinylbenzoquinone* (I).—The reaction between diethylamine (0·73 g.), acetaldehyde (0·22 g.), and chloranil (1·23 g.) in benzene (200 c.c.) gave the blue quinone (1·22 g., 80%), m. p. 126—132°. Crystallisation from benzene–light petroleum gave the pure compound, m. p. and mixed m. p. 131—133°.

2 : 3 : 5-*Trichloro*-6-2′-*dimethylaminovinylbenzoquinone*.—The reaction was carried out between dimethylamine (1·44 g. of a 25% solution in water), acetaldehyde (0·18 g.), and chloranil (1 g.) in benzene (150 c.c.). The purple dimethylaminoquinone was separated from the blue quinone by chromatography. The blue *quinone* (0·58 g., 50%) formed needles, m. p. 143—144° (Found: C, 42·95; H, 2·85; N, 4·95; Cl, 38·1. $C_{10}H_6O_2NCl_3$ requires C, 42·8; H, 2·85; N, 5·0; Cl, 37·9%).

2 : 3 : 5-*Trichloro*-6-2′-*morpholinovinylbenzoquinone*.—Morpholine (3·6 g.), acetaldehyde (0·9 g.), and chloranil (4·9 g.) in benzene (250 c.c.) at 25° gave the blue *quinone* (4·27 g., 70%), m. p. 155—157° (needles from benzene) (Found: C, 44·85; H, 3·1. $C_{12}H_{10}O_3NCl_3$ requires C, 44·7; H, 3·1%).

2 : 3 : 5-*Trichloro*-6-2′-*piperidinovinylbenzoquinone*.—Piperidine (0·86 g.), acetaldehyde (0·25 g.), and chloranil (1·23 g.) in benzene (70 c.c.) at 25° gave a product which on chromatography afforded the quinone (0·41 g., 25%), m. p. and mixed m. p. 144—146°, whose infrared spectrum was identical with that of material prepared from 1-ethylpiperidine (preceding paper).

2 : 3 : 5-*Trichloro*-6-2′-*pyrrolidinovinylbenzoquinone*.—This was prepared from pyrrolidine (0·72 g.), acetaldehyde (0·25 g.), and chloranil (1·23 g.) in benzene (75 c.c.). Crystallisation from toluene–light petroleum (b. p. 60—80°) gave the *quinone* (0·85 g., 55%) as needles, m. p. 130—133° (decomp.) (Found: C, 47·1; H, 3·05. $C_{12}H_{10}O_2NCl_3$ requires C, 47·0; H, 3·3%).

2 : 3 : 5-*Trichloro*-6-2′-*hexamethyleneiminovinylbenzoquinone*.—Hexamethyleneimine (1·3 g.), acetaldehyde (0·3 g.), and chloranil (1·6 g.) in benzene (85 c.c.) led to the blue *quinone* (1·32 g., 55%), m. p. 119—121° (from benzene–light petroleum) (Found: C, 49·95; H, 4·1. $C_{14}H_{14}O_2NCl_3$ requires C, 50·25; H, 4·2%).

2 : 3 : 5-*Trichloro*-6-2′-(*methylanilino*)*vinylbenzoquinone*.—From the rate of production of blue colour the reaction with methylaniline was relatively slow, and the mixture of amine (1·1 g.), acetaldehyde (0·23 g.), and chloranil (1·23 g.) in benzene (50 c.c.) was kept at 25° for 2 hr. Chromatography separated much unchanged chloranil from the blue *quinone* (85 mg.), m. p. 161—163° (needles from toluene–light petroleum) (Found: C, 52·5; H, 3·8. $C_{15}H_{10}O_2NCl_3$ requires C, 52·55; H, 3·95%).

2 : 3 : 5-*Trichloro*-6-[2-*di*-(2-*hydroxyethyl*)*aminovinyl*]*benzoquinone*.—A different procedure was devised for the reaction of diethanolamine which is insoluble in benzene. The amine (2·1 g.) in ethanol (10 c.c.) was added to acetaldehyde (0·44 g.) and chloranil (2·46 g.) in dioxan at 10°. The mixture was allowed to warm to 20° during 45 min., then water (500 c.c.), benzene (100 c.c.), and ethyl acetate (100 c.c.) were added. The organic layer was dried, concentrated, and filtered through deactivated alumina (20 g.), elution of the blue quinone being completed with ethyl acetate. Evaporation under reduced pressure gave a product from which unchanged chloranil was extracted with cold benzene. The crude compound, m. p. 122—127°, was crystallised from slightly aqueous acetone, to give the blue *quinone* (0·18 g.) as needles, m. p. 132—135° (Found: C, 41·85; H, 3·75. $C_{12}H_{12}O_4NCl_3$ requires C, 41·7; H, 3·5%).

3 : 5-*Dichloro*-6-2′-*diethylaminovinyl*-2-*methoxybenzoquinone* (III).—This reaction was carried out in a solution in pure dioxan (12 c.c.) of 2 : 6-dichloro-3 : 5-dimethoxybenzoquinone (0·237 g.), diethylamine (0·15 g.), and acetaldehyde (0·045 g.). The product was isolated in benzene, chromatographed, and crystallised from toluene–light petroleum, to give the *quinone* (0·125 g., 40%), m. p. 119—121° (Found: C, 51·6; H, 4·75. $C_{13}H_{15}O_3NCl_2$ requires C, 51·3; H, 4·95%).

2 : 5-*Dichloro*-3 : 6-*bis*-2-*diethylaminovinylbenzoquinone* (II).—A mixture of diethylamine (1·45 g.), acetaldehyde (0·45 g.), and chloranil (1·23 g.) in benzene (500 c.c.) was kept at 22° for 1 hr. The purple solution was processed as for the monosubstituted quinone, crystallisation from toluene–light petroleum finally affording the purple *quinone* (0·99 g., 55%) as granular prisms, m. p. 127—133° (Found: C, 58·35; H, 6·55; N, 7·05; Cl, 19·35. $C_{18}H_{24}O_2N_2Cl_2$ requires C, 58·5; H, 6·5; N, 7·55; Cl, 19·1%).

[8] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.

2-Chloro-3-2′-dimethylaminovinyl-1 : 4-naphthaquinone (IV; R = Me).—This compound was prepared by the general procedure starting from dimethylamine (1·42 g. of a 25% solution in water), acetaldehyde (0·18 g.), and 2 : 3-dichloronaphthaquinone (0·8 g.) in benzene (150 c.c.). Elution of the crude product from alumina (100 g.) with benzene first gave the red 2-chloro-3-dimethylaminonaphthaquinone (0·11 g., 13%), m. p. 82—88° [pure, m. p. 88—89° (lit., 85°) (Found: C, 61·2; H, 4·2; N, 5·75. Calc. for $C_{12}H_{10}O_2NCl$: C, 61·1; H, 4·25; N, 5·95%)], and then the purple *quinone* (0·32 g., 35%). The pure product separated from slightly aqueous acetone as needles, m. p. 158—161° (Found: C, 64·6; H, 4·65. $C_{14}H_{12}O_2NCl$ requires C, 64·25; H, 4·6%).

2-Chloro-3-2′-diethylaminovinyl-1 : 4-naphthaquinone (IV; R = Et).—Diethylamine (1·36 g.), acetaldehyde (0·4 g.), and 2 : 3-dichloronaphthaquinone (1 g.) in benzene (50 c.c.) were stirred at 20° for 1 hr. Chromatography on alumina (200 g.) (elution with benzene) gave the red *2-chloro-3-diethylaminonaphthaquinone* (16 mg., 1·5%), m. p. 57—59° [pure compound had m. p. 58—60° (Found: C, 64·05; H, 5·3; N, 5·4. $C_{14}H_{14}O_2NCl$ requires C, 63·75; H, 5·35; N, 5·3%)], followed by the purple quinone (1·197 g., 94%), m. p. 81—88°. Crystallisation from toluene–light petroleum gave the pure compound, m. p. and mixed m. p. 92—95°.

2-Chloro-3-(4-diethylaminobuta-1 : 3-dienyl)-1 : 4-naphthaquinone (VI).—Freshly prepared 1-diethylaminobutadiene (0·9 g.) was added to a solution of 2 : 3-dichloro-1 : 4-naphthaquinone (0·545 g.) in benzene (25 c.c.) at 20°. After 3 min. the product was isolated as before. The *quinone* (0·6 g., 80%) formed blue needles, m. p. 128—130° (from toluene–light petroleum) (Found: C, 68·95; H, 5·75. $C_{18}H_{18}O_2NCl$ requires C, 69·2; H, 6·0%).

This compound was prepared in lower yield from diethylamine and crotonaldehyde. The pure aldehyde (0·14 g.) and the amine (0·28 g.) were added to the dichloroquinone (0·227 g.) in benzene (15 c.c.) containing sodium sulphate (0·2 g.). After the mixture had been stirred for 70 min. at 20° it was filtered, concentrated under reduced pressure, and placed on deactivated alumina (20 g.). Elution with benzene (10 c.c.) gave the red 2-chloro-3-diethylaminonaphthaquinone (83 mg., 33%), m. p. 55—58° (from light petroleum). Further elution with benzene (40 c.c.) gave the blue quinone (68 mg., 21%) which after crystallisation from toluene–light petroleum had m. p. 125—127°, undepressed on admixture with the compound prepared by the first method. The infrared spectra were also identical.

Chloranil and n-Butylamine.—A solution of the quinone (0·5 g.) and the amine (0·6 g., excess) in benzene (50 c.c.) was kept at 20° for 24 hr. The mixture was evaporated to dryness and the residue washed with water, to give *2 : 5-bisbutylamino-3 : 6-dichlorobenzoquinone* (XIV) (0·50 g.), m. p. 201—202°. Crystallisation from dioxan–ethyl acetate gave pink plates, m. p. 202—203° (Found: C, 52·85; H, 6·3. $C_{14}H_{20}O_2N_2Cl_2$ requires C, 52·65; H, 6·3%). From a similar experiment with equimolar amounts of the quinone and amine, the same compound was obtained together with unchanged chloranil (separated chromatographically), and no mono-substituted compound could be detected.

2 : 5-Dichloro-3 : 6-dimethoxy-p-benzoquinone and n-Butylamine.—The amine (0·15 g., 2·05 mol.) was added to the quinone (0·237 g.) in benzene (15 c.c.) at 20°. The product began to separate as a pink precipitate within 1 min. After 30 min. the mixture was evaporated and the residue washed with water (these washings gave no precipitate with silver nitrate). Crystallisation from dioxan gave the foregoing quinone (XIV) (0·28 g., 88%), m. p. 202—203°. This compound was also obtained, with unchanged quinone (separated by chromatography), when equimolar quantities of amine and quinone were used.

2 : 5-Dichlorobenzoquinone and n-Butylamine.—The amine (0·15 g.) was added to the quinone (0·531 g.) in benzene (15 c.c.). The solution became red, and brown material was precipitated. After 15 min. the mixture was placed on a column of alumina (10 g.) which was developed with benzene. Evaporation of the eluate gave material which on crystallisation from dioxan gave the foregoing quinone (XIV) (70 mg., 22%), m. p. and mixed m. p. 201—202°.

2 : 6-Dichlorobenzoquinone and n-Butylamine.—The amine (0·45 g.) was added to a solution of the quinone (0·354 g.) in dioxan (10 c.c.). The solution became purple and then red. After 5 min. water was added until crystals (0·23 g., 81%), m. p. 169—171°, began to separate. Crystallisation from slightly aqueous dioxan gave *3-chloro-2 : 6-bisbutylaminobenzoquinone* as red needles, m. p. 172—174° (Found: C, 58·85; H, 7·4; N, 9·95. $C_{14}H_{21}O_2N_2Cl$ requires C, 59·05; H, 7·45; N, 9·85%).

Chloranil and Morpholine.—The amine (0·5 g.) was added to chloranil (0·246 g.) in dioxan (10 c.c.). After 10 min. methanol (10 c.c.) and water (1 c.c.) were added and after a further

15 min. the (almost pure) product (0·247 g., 70%) was collected. 2 : 5-Dichloro-3 : 6-dimorpholinobenzoquinone (XVI) formed brownish plates, m. p. 200—203° (Found: C, 48·35; H, 4·7. Calc. for $C_{14}H_{16}O_4N_2Cl_2$: C, 48·45; H, 4·65%).

The amine (87 mg.) in acetone (5 c.c.) was added to chloranil (0·246 g.) in dioxan (5 c.c.) and acetone (5 c.c.). After 10 min. the purple solution was washed with dilute hydrochloric acid and the product (0·11 g., 74%) was separated from unchanged chloranil by chromatography on deactivated alumina (50 g.). 2 : 3 : 5-*Trichloro*-6-*morpholinobenzoquinone* had m. p. 157—158° (from toluene–light petroleum) (Found: C, 40·3; H, 2·6. $C_{10}H_8O_3NCl_3$ requires C, 40·5; H, 2·7%).

2 : 5-*Dimethoxybenzoquinone and* n-*Butylamine*.—The quinone (0·136 g.), amine (0·45 g.), and dioxan (20 c.c.) were heated on a steam-bath for 90 min. The quinone slowly dissolved and the solution became orange-red. It was cooled and water was added until the product (0·111 g., 65%), m. p. 162—165°, crystallised. Pure 2 : 5-bisbutylamino-*p*-benzoquinone (XX) separated from aqueous dioxan as vermilion plates, m. p. 164—165° (Found: C, 67·3; H, 8·9; N, 11·4. Calc. for $C_{14}H_{22}O_2N_2$: C, 67·2; H, 8·85; N, 11·2%).

2 : 6-*Dimethoxybenzoquinone and* n-*Butylamine*.—A mixture of the quinone (0·272 g.), the amine (0·44 g.), and dioxan (10 c.c.) was heated on a steam-bath for 6 hr. The solvent was removed under reduced pressure and the residue was extracted with benzene at 20°, leaving starting material (77 mg.). The benzene solution was placed on deactivated alumina (15 g.). A purple band was eluted with benzene which on evaporation gave a product (112 mg., 50%), m. p. 120—128°. Crystallisation from methanol gave pure 2 : 5-*bisbutylamino*-3-*methoxy*-*p*-*benzoquinone* (XXIV) as brownish needles with a purple sheen, m. p. 134—135° (Found: C, 64·0; H, 8·5; N, 10·4. $C_{15}H_{24}O_3N_2$ requires C, 64·25; H, 8·55; N, 10·0%).

2 : 6-*Dichloro*-3 : 5-*dimethoxybenzoquinone and* n-*Butylamine*.—The amine (0·292 g.) was added to a solution of the quinone (0·237 g.) in dioxan (10 c.c.). A permanganate colour developed which after a few minutes changed to mauve. After 1 hr. the solution was washed with dilute hydrochloric acid, then chromatographed over deactivated alumina. A mauve band was eluted with benzene. Crystallisation from benzene–light petroleum gave 2-*chloro*-3 : 6-*bisbutylamino*-5-*methoxybenzoquinone* (XXII) (0·21 g., 67%) as purple needles, m. p. 133—134° (Found: C, 57·1; H, 7·45; N, 9·15. $C_{15}H_{23}O_3N_2Cl$ requires C, 57·2; H, 7·35; N, 8·9%).

The quinone (0·237 g.) in dioxan (10 c.c.) was treated with *n*-butylamine (90 mg., 1·2 mol.). After 5 hr. at 20°, the purple solution was evaporated under reduced pressure, the residue being extracted with benzene–light petroleum (1 : 1) and placed on deactivated alumina (20 g.). Benzene eluted the purple band, the product from which was crystallised from ethanol to give the 2-*butylamino*-3 : 5-*dichloro*-6-*methoxybenzoquinone* (XXV) (0·155 g., 56%), m. p. 89—94°. The pure compound formed purple needles, m. p. 97—99° (Found: C, 47·2; H, 4·85; Cl, 25·7. $C_{11}H_{13}O_3NCl_2$ requires C, 47·5; H, 4·7; Cl, 25·5%).

Reactions of 2 : 3 : 5-*Trichloro*-6-2′-*morpholinovinylbenzoquinone with Amines*.—*n*-Butylamine (0·148 g., 4 mol.) in dioxan (3 c.c.) was added to a solution of the quinone (0·161 g.) in dioxan (12 c.c.). The solution rapidly became green and after 5 min. water was added to precipitate the product. Crystallisation from benzene gave 3-*butylamino*-6-2′-*butylaminovinyl*-2 : 5-*dichlorobenzoquinone* (XIII) (95 mg.), m. p. 161—162° (Found: C, 55·95; H, 6·35. $C_{16}H_{22}O_2N_2Cl_2$ requires C, 55·65; H, 6·4%).

Dimethylamine (0·36 g. of a 25% solution in water) in dioxan (2 c.c.) was added to a solution of the quinone (0·161 g.) in dioxan (12 c.c.). The solution rapidly became olive-green and after 5 min. water was added. The precipitate was dried and crystallised from benzene, to give 2 : 5-*dichloro*-3-*dimethylamino*-6-2′-*morpholinovinylbenzoquinone* (XII) (0·122 g.), m. p. 167—168° (decomp.) (Found: C, 51·1; H, 4·9. $C_{14}H_{16}O_3N_2Cl_2$ requires C, 50·75; H, 4·85%).

Competitive Reaction of the Chloranils with n-*Butylamine*.—The amine (73 mg.) in benzene (1 c.c.) was added to a solution of *o*-chloranil (0·123 g.) and *p*-chloranil (0·123 g.) in benzene (20 c.c.). The mixture was kept for 24 hr. at 20°. Chromatography gave unchanged *p*-chloranil (0·11 g., 89%) but no *o*-compound.

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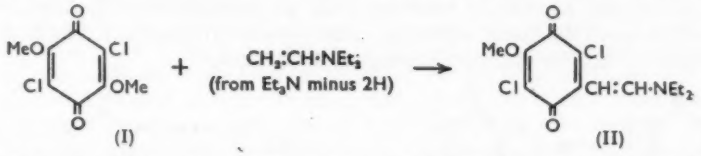
983. *Amine Oxidation. Part III.*[1] *A Test Reaction for the Dehydrogenation of Triethylamine. The Reactions of Some Tertiary Amines with Benzoyl Peroxide.*

By D. Buckley, Sonia Dunstan, and H. B. Henbest.

Dehydrogenation of triethylamine (or other suitable tertiary amines) by an oxidising agent can be detected by the formation of a blue quinone if the reaction is carried out in the presence of a dichlorodimethoxy-*p*-benzoquinone. One of the effective reagents is benzoyl peroxide, and some of its reactions with tertiary amines are discussed.

When triethylamine is added to a dilute (yellow) solution of 2 : 5-dichloro-3 : 6-dimethoxybenzoquinone (I) in benzene the colour deepens somewhat owing to complex formation, but in the absence of strong light the solution does not become blue, *i.e.*, a dialkylaminovinyl-quinone, which could be formed by dehydrogenation of the amine followed by coupling of the resulting enamine with the starting quinone,[1] is not produced. However, on addition of some benzoyl peroxide a blue colour developed rapidly, owing to formation



(I) (II)

of the diethylaminovinyl-quinone (II). The conclusion follows that benzoyl peroxide is effective in dehydrogenating triethylamine to diethylvinylamine, which then displaces a methoxyl group from the quinone (I) to give the blue compound (II): this displacement also takes place with other nucleophils, *e.g.*, *n*-butylamine.[2] Violently exothermic reactions often take place on addition of benzoyl peroxide to tertiary amines,[3] but controlled reactions can be carried out in more dilute solution and secondary amines and carbonyl compounds can be obtained after hydrolysis [4,5] (cf. below). The present reaction, in the presence of the quinone (I), constitutes the first demonstration that an enamine can be formed from a tertiary amine and the peroxide.

By using development of a blue colour from the quinone (I) and triethylamine as a test for enamine formation from the tertiary amine, it has been shown that *N*-bromosuccinimide and 3 : 3′ : 5 : 5′-tetrachlorodiphenoquinone also dehydrogenate the amine in dilute benzene solution. Manganese dioxide gave a negative reaction, but the principle has been used to detect the occurrence of dehydrogenation on treatment of diethylaniline with the dioxide in the presence of chloranil (which alone does not readily dehydrogenate diethylaniline), and a blue quinone was isolated.[6]

The test reaction with *N*-bromosuccinimide was exceptional in that the blue colour did not develop gradually but appeared suddenly after several minutes. Separate experiments showed that the blue quinone (II) was decolorised by *N*-bromosuccinimide in benzene solution, and thus the blue colour appears only when all of the bromo-imide has reacted (see also the following paper).

The observations that triethylamine is dehydrogenated by chloranil but not by *p*-benzoquinone [1] at room temperature are paralleled by the positive and negative result

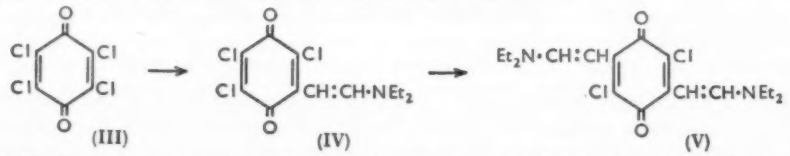
[1] Part II, Buckley, Dunstan, and Henbest, *J.*, 1957, 4880.
[2] Buckley, Henbest, and Slade, preceding paper.
[3] Nozaki and Bartlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1686; 1947, **69**, 2299; Horner and Schwenk, *Annalen*, 1950, **566**, 69.
[4] Paolini and Ribet, *Gazzetta*, 1932, **62**, 1041; Gambarjan and Kazarjan, *J. Gen. Chem.* (*U.S.S.R.*), 1933, **2**, 222.
[5] Horner and Kirmse, *Annalen*, 1955, **597**, 48.
[6] Henbest and Thomas, *J.*, 1957, 3032.

given respectively in the above test reaction by the tetrachlorodiphenoquinone and by diphenoquinone. In the case of chloranil, dehydrogenation of the tertiary amine can be detected by the formation of a blue quinone without the addition of a second quinone such as (I). However the presence of the quinone (I) is essential for colour production from the tetrachlorodiphenoquinone as the latter quinone (in contrast to chloranil) is not substituted by the enamine to give a coloured product.

Reactions of Benzoyl Peroxide with Amines containing an $R_2N{\cdot}CH_2{\cdot}CH_2$ *Grouping.*—In the reaction of triethylamine (excess) with benzoyl peroxide in the presence of the quinone (I) the yield of blue quinone (II) was proportional to the amount of peroxide added up to a peroxide : quinone ratio of 1 : 1. A similar relation was found for the corresponding reaction in the presence of chloranil (III), allowance being made for the concurrent (slower) dehydrogenation caused by this quinone. The results are consistent with a dehydrogenation as follows:

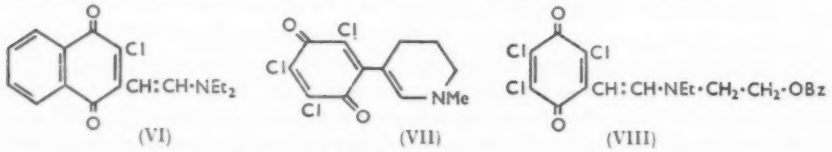
$$Et_3N + Bz_2O_2 \longrightarrow Et_2N{\cdot}CH{:}CH_2 + 2BzOH$$

The yields of blue compound from quinone (I) were consistently lower than those of the corresponding product from chloranil (III). This is probably due to the lower reactivity of the former quinone towards the nucleophilic enamine, the chances of the enamine undergoing alternative reactions such as polymerisation (encouraged by the presence of the peroxide) being increased. The quinone (I) also reacted more slowly than chloranil with the simpler nucleophilic reagent, diethylamine.



(III) (IV) (V)

When increasing amounts of benzoyl peroxide were added to chloranil and an excess of triethylamine in benzene solution, the blue colour initially formed was replaced by a purple colour due to the formation of the bisdiethylaminovinylquinone (V). The pure compound was best obtained by this method starting from the blue quinone (IV); it was identical with the product formed by the acetaldehyde–diethylamine method.[2]



(VI) (VII) (VIII)

The slow dehydrogenation of triethylamine by 2-chloronaphtha-1 : 4-quinone and the formation of the purple quinone (VI) in low yield has been described.[1] By using benzoyl peroxide as the dehydrogenating reagent a much better yield of the same quinone (VI) was obtained more quickly. From the point of view of the production of dialkylaminovinyl-quinones, generation of the necessary enamine by the amine–peroxide reaction is of most value where the usually more convenient aldehyde–secondary amine method [2] is not easily applied: synthesis of the blue quinone (VII) by dehydrogenating 1-methylpiperidine with benzoyl peroxide in the presence of chloranil provides such an example, the amino-aldehyde necessary for the alternative method of synthesis not being easily available, and chloranil itself not readily introducing a double bond into a piperidine ring.[1]

Diethylaminoethanol with benzoyl peroxide and chloranil gave the blue quinone (IV) in 10% yield, corresponding to dehydration of the initial amine. Its benzoate gave, in contrast, the blue quinone (VIII) in 10% yield.

Reactions of Benzoyl Peroxide with Amines of the $Me_2N{\cdot}CH_2Ar$ *Type.*—These amines cannot form enamines on dehydrogenation, but hydrolysis of an intermediate,

$Me_2N{\cdot}CHAr{\cdot}OBz$, should give a carbonyl compound and a secondary amine. Previous work [4, 5] on the tertiary amine–benzoyl peroxide reaction has been concerned with this overall process, which can take place in principle with all amines containing an $\rangle N{\cdot}CH\langle$ grouping.

In the present study the oxidation of some unsymmetrical amines of the benzyldimethylamine type was examined, attention being directed towards the amounts of aromatic aldehydes produced. The yields show that there is in each case some preference for oxidation to be directed into the benzyl grouping, and that relatively small differences in yield result from variation of a *para*-substituent.

Comments.—To aid a search for intermediates the infrared absorptions of mixtures of amine and benzoyl peroxide were determined in the 1900—1600 cm.$^{-1}$ region. With one exception, diminution of the twin peaks given by benzoyl peroxide at 1785 and 1762 cm.$^{-1}$ was accompanied by development of a broader peak near 1705 cm.$^{-1}$. The new peak may be attributed to intermediates of structure, $R_2N{\cdot}CHR'{\cdot}OBz$, and/or to benzoic acid, separate experiments showing that the presence of a tertiary amine did not appreciably alter the position of the carbonyl peak of this acid.

Rates were compared by determining the time in each reaction for the intensities of the diminishing 1762 cm.$^{-1}$ peroxide peak and the rising 1705 cm.$^{-1}$ peak to become equal. Thus the reaction velocity was found to depend on the steric accessibility of the nitrogen atom in the amine. In triethylenediamine, $N[CH_2{\cdot}CH_2]_3N$, the nitrogen atoms are very exposed but intermediates of the type $[R_2N{:}CHR']^+$ should be formed only with difficulty or not at all (Bredt's rule): in line with this, reaction was very rapid—under the standard conditions the 1762 cm.$^{-1}$ peak disappeared before measurements could be taken—and a peak developed at 1780 as well as at 1705 cm.$^{-1}$. The peak at 1780 cm.$^{-1}$ may possibly be attributed to the cation, $\{N[CH_2{\cdot}CH_2]_3N{\cdot}Bz\}^+$, a type of structure not likely to be stable in simpler amines where loss of benzoic acid can take place without difficulty. The 1780 cm.$^{-1}$ peak diminished gradually: the final products have not been investigated.

These results are consistent with a heterolytic mechanism involving the displacement of benzoate anion from the peroxide by a nucleophilic trialkylamine molecule. An analogy may be drawn with the reaction of benzoyl peroxide with the strongly nucleophilic alkoxides.[7]

$$R_2N{\cdot}CH_2R' + Bz_2O_2 \longrightarrow [R_2N(CH_2R'){\cdot}OBz]^+ + BzO^-$$

$$\uparrow\downarrow -BzOH$$

$$\text{Enamine}^* \xleftarrow{-H^+} [R_2N{:}CHR']^+ \xrightarrow{H_2O} R_2NH + R'{\cdot}CHO$$

* If R′ = Me or another group containing CH.

It has been suggested before that the reactions of dialkylanilines proceed by such a heterolytic mechanism,[8] but on the other hand formation of radical intermediates in tertiary amine–benzoyl peroxide reactions has been urged.[5] Further discussion is deferred until more evidence is available.

Experimental

Solvents and reagents were purified: it was particularly important to remove acetal impurities from dioxan.

Test Reaction.—A few mg. of dehydrogenating reagent were added to 5 c.c. of a freshly prepared benzene solution of 2 : 5-dichloro-3 : 6-dimethoxy-*p*-benzoquinone (0·04M) and triethylamine (0·08M). Development of a blue colour within 30 min. in subdued light indicated dehydrogenation. Positive tests were given by benzoyl peroxide, 3 : 3′ : 5 : 5′-tetrachlorodiphenoquinone and *N*-bromosuccinimide: negative tests by manganese dioxide, iodine, di-*tert.*-butyl peroxide, and diphenoquinone.

Dehydrogenation of Triethylamine.—(a) *In the presence of* 2 : 5-*dichloro*-3 : 6-*dimethoxy*-p-*benzoquinone.* The amine (0·8 g.) was added to a solution of the quinone (0·41 g.) and benzoyl

[7] Doering and Greenbaum, quoted by Greenbaum, Denny, and Hoffmann, *J. Amer. Chem. Soc.*, 1956, **78**, 2563.

[8] Imoto and Takemoto, *J. Polymer Sci.*, 1956, **19**, 579.

peroxide (0·484 g.) in benzene (25 c.c.). After 1·5 hr. the blue solution was filtered from triethylamine hydrochloride (90 mg.), m. p. 254—255° (sealed tube) after crystallisation from *iso*propyl alcohol, and washed with dilute hydrochloric acid and dilute aqueous sodium hydroxide. Filtration of the blue solution through deactivated alumina (10 g.) followed by crystallisation of the product from light petroleum (b. p. 60—80°) gave the blue 2 : 5-*dichloro*-3-2′-*diethylaminovinyl*-6-*methoxybenzoquinone* (II) (0·11 g.) as needles, m. p. 109—110° (Found: C, 51·15; H, 4·95. $C_{13}H_{15}O_3NCl_2$ requires C, 51·3; H, 4·95%).

(b) *In the presence of 2-chloronaphthaquinone.* Benzoyl peroxide (1·22 g.) in benzene (100 c.c.) was added to a solution of the quinone (0·96 g.) and triethylamine (1·5 g.) in benzene (100 c.c.). After 1 hr. at 20°, the deep purple solution was washed with dilute sodium hydroxide solution until benzoic acid had been removed. The benzene solution was filtered through deactivated alumina (25 g.) and evaporated. The residue was dissolved in acetone and water was added to induce crystallisation. 2-Chloro-3-2′-diethylaminovinylnaphtha-1 : 4-quinone (0·35 g., 48%) had m. p. and mixed m. p. 95—99° and light absorption properties identical with those of the product made by alternative methods (two previous papers).

(c) *In the presence of the blue quinone* (IV). Benzoyl peroxide (0·73 g.) was added to a solution of the quinone (0·92 g.) and triethylamine (1·2 g.) in benzene (90 c.c.). After 3 hr. at 20°, the purple solution was worked up in the usual way, and the product chromatographed on deactivated alumina. Crystallisation from toluene–light petroleum gave the quinone (V) (0·537 g.), m. p. 129—130°. M. p. and light absorption comparisons confirmed its identity with the compound prepared as in the previous paper.

Dehydrogenation of 1-*Methylpiperidine.*—A solution of chloranil (3 g.), benzoyl peroxide (3 g.), and the amine (5 g.) in benzene (700 c.c.) was kept at 15° for 2·5 hr., then washed with N-sulphuric acid and 5% sodium hydroxide solution, dried, and evaporated under reduced pressure. Crystallisation from toluene–light petroleum gave the blue 2 : 3 : 6-*trichloro*-5-(1 : 4 : 5 : 6-*tetrahydro*-1-*methyl*-3-*pyridyl*)*benzoquinone* (VII) (0·45 g.), m. p. 105—107° (decomp.) (Found: C, 47·0; H, 3·4; N, 4·85. $C_{12}H_{10}O_2NCl_3$ requires C, 47·0; H, 3·3; N, 4·55%).

Dehydrogenation of 2-*Diethylaminoethyl Benzoate.*—The amino-ester (9·7 g.) was added to chloranil (4·91 g.) and benzoyl peroxide (4·84 g.) in benzene (700 c.c.) at 20°. The solution became green, then blue. The change in concentration of blue quinone was followed spectrophotometrically at 6300 Å and the reaction was shown to be complete within 40 hr. The solution was decanted from green tar, washed with 0·2N-sodium hydroxide, water, 0·2N-hydrochloric acid, and water and dried (Na_2SO_4). The product was chromatographed on deactivated alumina (100 g.). Elution with benzene–light petroleum (1 : 2) yielded unchanged chloranil, followed by the principal blue band. Crystallisation of this blue compound (0·9 g.) from toluene–light petroleum gave 2-[2-(N-2-*benzoyloxyethyl*-N-*ethylamino*)*vinyl*]-3 : 5 : 6-*trichlorobenzoquinone* (VIII), m. p. 135—136·5° (Found: C, 53·7; H, 4·0; N, 3·4. $C_{19}H_{16}O_4NCl_3$ requires C, 53·2; H, 3·75; N, 3·25%), with infrared bands (in Nujol) at 1710 (benzoate-carbonyl) and 1670 cm.$^{-1}$ (non-conjugated quinone-carbonyl).

From a similar reaction between 2-diethylaminoethanol (8 g.), chloranil (5 g.), and benzoyl peroxide (5 g.) in benzene at 20° for 18 hr. (reaction complete), the blue quinone (IV) (0·59 g.) was obtained after chromatography; its properties including infrared absorption were identical with those of previous samples.

Formation of Aldehydes from Tertiary Amines.—A solution of the amine (0·002 mole) in the desired solvent (5 c.c.) was added to benzoyl peroxide (0·001 mole) in the same solvent (5 c.c.) at 20°. The reaction was taken as complete when the bulk of the peroxide had been consumed, as indicated by the greatly diminished intensity of the blue colour produced by a sample on mixing with triethylamine and 2 : 5-dichloro-3 : 6-dimethoxy-*p*-benzoquinone (test reaction as above). The yields of aldehydes were estimated as 2 : 4-dinitrophenylhydrazones after addition of an excess of the reagent sulphate in methanol (see Table).

Amine	Solvent	Reaction time (hr.)	2 : 4-Dinitrophenylhydrazone (%)
$Ph{\cdot}CH_2{\cdot}NMe_2$	Benzene	9	56, 53
$Ph{\cdot}CH_2{\cdot}NMe_2$	Dioxan	8	47
p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2$	Benzene	1·5	56, 60
p-$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2$	Benzene	5	47
NPr^n_3	Dioxan–H_2O (9 : 1)	1·5	39 *

* Unused peroxide (60%) was recovered from this experiment.

Dinitrophenylhydrazines of the following were obtained (each gave a satisfactory analysis): benzaldehyde, m. p. 242—244·5° (from dioxan–ethyl acetate), *p*-anisaldehyde, m. p. 254—255° (from dioxan), *p*-nitrobenzaldehyde, m. p. 334° (from pyridine–methanol), and propionaldehyde, m. p. 153—157° (from ethanol).

Comparative Reaction Rates.—Equal volumes of solutions of the amine (0·4M) and benzoyl peroxide (0·2M) in benzene were mixed, introduced immediately into a 1 mm. cell, and the infrared absorption in the 1900—1600 cm.$^{-1}$ range repeatedly determined. As the peaks at 1785 and 1762 cm.$^{-1}$ due to benzoyl peroxide diminished, a new maximum at 1705 cm.$^{-1}$ developed: the times at which the heights of the 1762 and 1705 cm.$^{-1}$ peaks became equal are as annexed, the temperature of the mixture being in each case 20°.

Amine	Time (min.)	Amine	Time (min.)
Triethylenediamine	<1	NPr^n_3	9·25
NMe_3	1·5	$Ph{\cdot}CH_2{\cdot}NMe_3$	9·75
NEt_3	8·0	$N(CH_2Ph)_3$	>19 days

Within 1 hr., the solutions from those amines (triethylamine, tripropylamine) which can give enamines became yellow, then orange, then brown. The other reaction solutions remained colourless.

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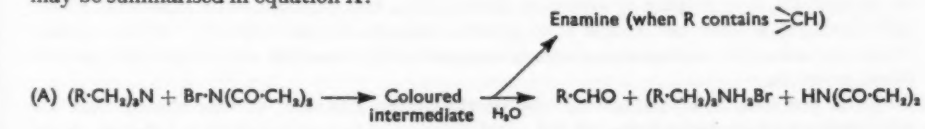
984. *Amine Oxidation. Part IV.*[1] *Reactions of Tertiary Amines with N-Bromosuccinimide: the Formation of Aldehydes and Secondary Amines.*

By SONIA DUNSTAN and H. B. HENBEST.

In appropriate experimental conditions, good yields of aldehydes and secondary amines can be obtained from tertiary amines and *N*-bromosuccinimide. The course of reaction can be followed by the appearance and disappearance of a coloured intermediate. An amine (triethylenediamine) in which inversion at nitrogen is prohibited gave a crystalline adduct.

IN the previous paper [1] it was reported that *N*-bromosuccinimide effected the dehydrogenation of triethylamine because a blue dialkylaminovinyl-quinone was formed in the presence of a dichlorodimethoxy-*p*-benzoquinone. This led to the present more detailed investigation of the tertiary amine–bromo-imide reaction, the results of which for many amines may be summarised in equation A:



Nothing definite is known at present about the structures of the coloured intermediates or of their possible relation to conjugate acids, $R{\cdot}CH{:}N^+(CH_2R)_2$, from which the hydrolysis products or the enamines (where possible) could also be formed.

*Tri-*n*-propylamine.*—No attempt was made to isolate the (very reactive) enamine which, on the basis of the colour test,[1] can be formed by reaction of the amine with *N*-bromosuccinimide. Attention was focused instead on isolating the more stable products (propionaldehyde and di-*n*-propylamine) to be expected from hydrolysis of the enamine or a related intermediate. For this reason the reactions were carried out in dioxan containing 10% of water. On mixing solutions of the reactants a strong yellow colour appeared

[1] Buckley, Dunstan, and Henbest, preceding paper.

which more slowly faded to give a colourless solution. During the fading the colour given in a starch–iodide test for " positive halogen " also diminished, becoming very faint as the solution became colourless. Propionaldehyde was obtained as its 2 : 4-dinitrophenylhydrazone in 63% yield and di-*n*-propylamine in over 80% yield (estimated by titration and by the isolation of the toluene-*p*-sulphonyl derivative).

Tribenzylamine.—Most of the reactions between this amine and *N*-bromosuccinimide were carried out in benzene with a view to attempt the isolation of the expected coloured intermediate (decomposition into an enamine being impossible in this case). Admixture of solutions of the reactants in benzene in an open flask produced a deep orange colour, which faded while dibenzylamine hydrobromide and succinimide were precipitated: under these conditions atmospheric moisture was responsible for the fading. From the final colourless mixture, benzaldehyde (85—90% as its 2 : 4-dinitrophenylhydrazone) and dibenzylamine (85%) were isolated. The aldehyde and the secondary amine were each obtained in 90% yields from a similar reaction in aqueous dioxan.

By conducting the reaction in benzene with the exclusion of water, the intermediate complex was obtained as a deep orange oil giving a positive starch–iodide test. The infrared spectrum of this product was similar to that of a mixture of the starting materials, although there were some changes in positions and intensities of the bands. Hydrolysis of the coloured oil gave benzaldehyde and dibenzylamine.

Benzyldimethylamine.—This was the only unsymmetrical amine studied: benzaldehyde (65%) was isolated after a reaction in benzene in an open flask. This yield shows that the choice of alkyl group oxidised is not random. The yield of benzaldehyde is similar to that obtained on oxidation of this amine with benzoyl peroxide.[1]

Triethylenediamine.—In an attempt to obtain a more stable intermediate, the reaction between triethylenediamine, $N[CH_2 \cdot CH_2]_3 \cdot N$, and *N*-bromosuccinimide was examined. When benzene was used as solvent, a colourless crystalline compound (~80%) separated rapidly which gave analyses for an adduct, $C_6H_{12}N_2,2(CH_2 \cdot CO)_2NBr$. This, like the orange intermediate obtained from tribenzylamine, gave a positive starch–iodide test and gave an infrared spectrum similar to the combined spectra of its components. Whether the colourless product from the diamine and the orange oil from tribenzylamine represent (despite the difference in colour) analogous stages in the respective reactions, or whether the colourless product represents a stage in the general reaction preceding the formation of the usual coloured intermediate (its special geometry preventing the further change), cannot be decided with certainty at present.

By comparing our results with previous work,[2,3] it may be concluded that the most effective conversion of a tertiary amine into an aldehyde and a secondary amine can be achieved (*a*) when one mole of each reactant is used (cf. equation A), (*b*) when both reactants are in solution, thus helping to moderate the reaction, and (*c*) when water is present for the hydrolysis stage; the last factor is of greatest importance for aliphatic tertiary amines where the coloured intermediates can decompose to an enamine and thence give rise to other products.

In a previous brief study[3] of the triethylamine reaction, it was shown that the precipitate formed on addition of the solid bromo-imide (one mol.) to a solution of the amine (two mols.) in carbon tetrachloride at 0° was a mixture of triethylamine hydrobromide and succinimide. The reaction under these conditions can be written as:

$$2Et_3N + Br \cdot N(CO \cdot CH_2)_2 \longrightarrow Et_2N \cdot CH{:}CH_2 + Et_3NHBr + HN(CO \cdot CH_2)_2$$

the second molecule of triethylamine effectively taking up the molecule of hydrogen bromide from the enamine precursor. On this basis the quoted yields of hydrobromide and succinimide are 48% and 74% respectively. If some addition of bromo-imide to the enamine occurs, these yields become higher.

[1] Cosgrove and Waters, *J.*, 1949, 907.
[2] Braude and Waight, *J.*, 1952, 1116.

In another investigation,[2] the solid bromo-imide was added to solutions of amines in a non-polar solvent, and water was afterwards added, giving low yields of aldehydes and secondary amines. The isolation of some glyoxal (as its bis-2 : 4-dinitro-osazone) from the triethylamine reaction is of interest, for it could clearly arise by further reaction of the bromo-imide with the enamine ($Et_2N{\cdot}CH{:}CH_2$) produced by decomposition of the coloured type of intermediate (cf. equation A), followed by unexceptional hydrolysis and oxidation during the isolation. The initial product, $(CH_2{\cdot}CO)_2N{\cdot}CH(NEt_2){\cdot}CH_2Br$, to be expected from the bromo-imide–enamine reaction would be analogous to those isolated $[(CH_2{\cdot}CO)_2N{\cdot}CH(OR){\cdot}CH_2Br]$ on addition of the bromo-imide to vinyl ethers.[4]

Experimental

Purified materials were used. It is particularly important to remove acetal impurities from dioxan.

*Tri-*n*-propylamine.*—The amine (0·286 g., 0·002 mole) in dioxan (9 c.c.) and water (1 c.c.) was added to *N*-bromosuccinimide (0·356 g., 0·002 mole) in the same solvent mixture (10 c.c.) at 20°. A strong yellow colour developed immediately and soon began to fade. After 2 min. the solution was almost colourless and the starch–iodide test was only faintly positive and an excess of methanolic 2 : 4-dinitrophenylhydrazine sulphate reagent was then added. The derivative was isolated with benzene and chromatographed on bentonite–kieselguhr.[5] Elution with chloroform gave a small amount of a yellow compound, m. p. 132—136° (after many crystallisations from ethanol). Elution with chloroform–ethanol (19 : 1) gave propionaldehyde 2 : 4-dinitrophenylhydrazone (56, 65, 68%), m. p. and mixed m. p. 153—156° (from ethanol) (Found: C, 45·6; H, 4·0; N, 23·7. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·25; N, 23·5%).

For the estimation of amines another reaction mixture was partially evaporated under reduced pressure, treated with an excess of aqueous sodium carbonate solution, and distilled into an excess of 0·1N-hydrochloric acid which was finally back-titrated with standard alkali to pH 5: the total amine recovery was 98—99%. Di-*n*-propylamine hydrochloride was isolated from another experiment by evaporating the acid solution (containing the amine distillate) to dryness: crystallisation from acetone gave the hydrochloride, m. p. 268—269° (sealed tube) (Found: C, 52·2; H, 11·6; N, 10·7; Cl, 25·6. Calc. for $C_6H_{16}NCl$: C, 52·4; H, 11·6; N, 10·2; Cl, 25·8%). A similar procedure was used to estimate unchanged tertiary amine, except that toluene-*p*-sulphonyl chloride was added to the alkaline solution before the distillation into acid. Unchanged tri-*n*-propylamine (11%; average of two experiments) was obtained: obviously this could be decreased by using slightly more bromo-imide. The yield of di-*n*-propylamine was therefore 87%, and this was confirmed by ether-extraction of the residual mixture from the last distillation, crude *NN*-di-*n*-propyltoluene-*p*-sulphonamide being obtained in this yield. The pure *sulphonamide* had m. p. 31—31·5° (from ether–light petroleum) (Found: C, 61·1; H, 8·1; N, 5·7. $C_{13}H_{21}O_2NS$ requires C, 61·2; H, 8·25; N, 5·5%).

Tribenzylamine.—(a) *Reactions in benzene.* The amine (0·574 g., 0·002 mole) in benzene (5 c.c.) was added to a solution of *N*-bromosuccinimide (0·357 g., 0·002 mole) in the minimum amount of benzene. An intense orange colour developed rapidly, but within a few minutes this began to fade and a mixture of dibenzylamine hydrobromide and some succinimide began to be precipitated. When the reaction was complete (negative starch–iodide test), the mixture was filtered (see below) into a methanolic solution of 2 : 4-dinitrophenylhydrazine sulphate. The 2 : 4-dinitrophenylhydrazone was collected; a further small amount was isolated by addition of water and benzene to the mother-liquor and chromatography of the benzene-soluble material on a column of bentonite–kieselguhr. The yields of benzaldehyde derivative were 85—90%; after crystallisation from dioxan–ethyl acetate the m. p. and mixed m. p. was 243—244° (Found: C, 54·5; H, 3·6; N, 19·9. Calc. for $C_{13}H_{10}O_4N_4$: C, 54·55; H, 3·5; N, 19·6%). The precipitate from the reaction mixture consisted predominantly of dibenzylamine hydrobromide: crystallisation from ethanol–ether gave the pure hydrobromide, subliming at 254° (Found: C, 60·5; H, 5·75; N, 4·7; Br, 28·8. Calc. for $C_{14}H_{14}NBr$: C, 60·4; H, 5·75; N, 5·05; Br, 28·8%).

If the filtrate from the reaction mixture was evaporated to a small bulk and benzene–light

[4] Paul and Tchelitcheff, *Compt. rend.*, 1953, **236**, 1968.
[5] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.

petroleum (1 : 1) was added, succinimide (+ some residual hydrobromide) was precipitated. The combined hydrobromide and succinimide precipitates were treated with ether and 0·2N-sodium hydroxide. The product from the ether extract was chromatographed on alumina. Elution with benzene–light petroleum (1 : 2) gave unchanged tribenzylamine (<2% from different experiments). Elution with ether gave dibenzylamine (85% yield), detected in the eluate (*a*) by universal indicator paper, and (*b*) by immediate production of a blue colour on treatment with a benzene solution of chloranil and acetaldehyde.[6] For general preparative purposes the partially evaporated reaction mixture can be treated with light petroleum to complete the separation of secondary amine hydrobromide (+ succinimide) which, after being washed with light petroleum, can be treated with alkali and the secondary amine then isolated with ether.

Addition of methanol (0·02 mole) to the amine solution before admixture with the bromo-imide caused the yields of benzaldehyde and dibenzylamine to fall to 51 and 63% respectively, and the yield of recovered tribenzylamine to change to 34%.

The reaction in benzene (see above) was also performed under dry nitrogen, and when the intense orange colour had developed the solution was evaporated under reduced pressure. During this operation an orange oil separated as a lower layer. On exposure to moist air this quickly began to change to a white solid (hydrobromide + succinimide), but by rapid manipulation it was possible to place some of the oil between rock-salt plates for determination of the infrared spectrum.

(b) *Reactions in dioxan.* These were carried out as described for benzene, except that a smaller quantity of solvent could be used to dissolve the bromo-imide: the same colour changes were observed during the reaction. With a 1 : 1 molar ratio of amine and bromo-imide, benzaldehyde 2 : 4-dinitrophenylhydrazone, dibenzylamine, and tribenzylamine were obtained in 90, 90, and 2% yield respectively, the reaction time being 5 hr. (solution then colourless).

In another experiment an amine : bromo-imide ratio of 1 : $\frac{2}{3}$ was used. The solution then remained yellow for much longer and precipitation of hydrobromide was retarded. After 24 hr. benzaldehyde 2 : 4-dinitrobenzylhydrazone (74%) was isolated.

Reaction with Dimethylbenzylamine.—The amine (0·27 g., 0·002 mole) in benzene (10 c.c.) was added to a solution of the bromo-imide (0·356 g., 0·002 mole) in benzene (40 c.c.) at 20° in an open flask. A yellow colour developed rapidly which then faded slowly, but in this case very little hydrobromide crystallised. When the reaction was complete (negative starch–iodide test on colourless solution), benzaldehyde 2 : 4-dinitrophenylhydrazone (64, 66%) was isolated as before.

Reaction with Triethylenediamine.—A solution of *N*-bromosuccinimide (0·356 g., 0·002 mole) in benzene (15 c.c.) was added to the amine (0·112 g., 0·001 mole) in benzene (5 c.c.) at 20° in an open flask. Within a minute a colourless product began to be precipitated from the colourless solution. After 1·5 hr. the crystalline *adduct* (83%) was collected; it had m. p. 109—111° (decomp.) (Found: C, 36·9, 36·9; H, 4·35, 4·5; N, 11·9; Br, 34·3. $C_{14}H_{20}O_4N_4Br_2$ requires C, 35·9; H, 4·25; N, 12·0; Br, 34·2%). This compound did not crystallise without decomposition, even at low temperatures; it also decomposed slowly on storage at 0° *in vacuo* in the dark.

The filtrate from the preparation of the adduct gave a weak positive starch–iodide test, apparently owing to the slight solubility of the compound as the adduct itself gave a very strong positive test. The adduct gave no precipitate of silver bromide on addition to silver nitrate in dilute nitric acid. As far as such tests were concerned the properties of the adduct were qualitatively indistinguishable from those of *N*-bromosuccinimide. The same adduct (same tests given) was obtained (lower yield) when equimolar quantities of amine and bromo-imide were used in the preparation. The infrared spectrum of the adduct in Nujol showed peaks at 1732 (w), 1680 (s), 1310 (m), 1245 (w), 1195 (ms), 1060 (w), and 790 (m) cm.$^{-1}$. *N*-Bromosuccinimide under the same conditions gave peaks at 1762 (w), 1700 (s), 1330 (m), 1255 (w), 1188, 1172 (ms), and 818 (w) cm.$^{-1}$. The peak at 1060 cm.$^{-1}$ given by the adduct appears to be associated with the amine which also gives a band at this position.

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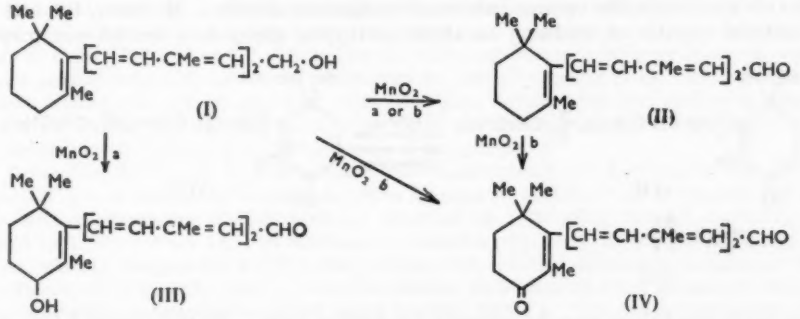
[6] Buckley, Henbest, and Slade, *J.*, 1957, 4891.

985. *Studies in the Polyene Series. Part LII.* Oxidation of Vitamin A_1 and Retinene$_1$ by Manganese Dioxide.*

By H. B. Henbest, E. R. H. Jones, and T. C. Owen.

From a study of oxidation by manganese dioxide, it has been shown that oxygenation of the methylene group at the 3-position in the terminal ring may occur with β-ionylidene compounds, and oxo-derivatives of vitamin A_1 and retinene$_1$ have thus been prepared.

The best procedure for preparing retinene$_1$ (II) is by oxidation of vitamin A_1 (I) by the elegant and convenient manganese dioxide method.[1,2] In agreement with Wald [3] it was found that reaction was fast enough to be effected by merely filtering a solution of the alcohol in light petroleum through a tube containing the oxidising agent, and most of the experiments described below were carried out by this technique. Various samples of manganese dioxide gave different yields of retinene$_1$. The use of dioxide prepared by a modification of the procedure described by Attenburrow *et al.*[4] (see p. 4911) afforded almost quantitative yields of the aldehyde by the percolation technique. " Precipitated manganese dioxide " (B.D.H.) [MnO_2(a) on the chart] gave about an 80% yield of retinene together with 15% of a compound which was more difficult to elute. The latter was purified by chromatography but did not crystallise. Its ultraviolet absorption ($\lambda_{max.}$ 3700 Å in EtOH) was similar to that given [5] for a product (" 545 mμ chromogen "—antimony trichloride colour) obtained in a similar manner, and for which a 3-hydroxyretinene$_1$ structure (III) was favoured. This has been confirmed since (*a*) the infrared spectrum shows the presence of a hydroxyl group, (*b*) $\lambda_{max.}$ in the ultraviolet is displaced 100 Å to shorter wavelength from that of the parent aldehyde retinene$_1$—a similar shift was observed [6] with the simpler compounds, β-ionone and 3-hydroxy-β-ionone—and (*c*) interconversion with 3-oxoretinene$_1$ (IV) was achieved (see below).

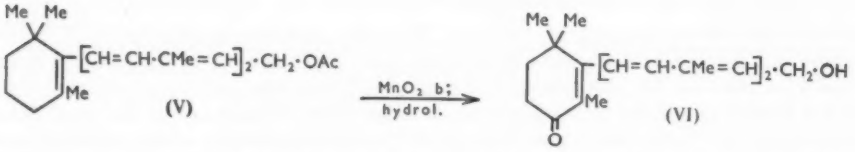


Another commercial sample of manganese dioxide (supplied by J. Woolley, Sons & Co. Ltd., and prepared under acidic conditions: see p. 4911) gave even more unusual results. When a pentane solution of vitamine A_1 was filtered through this material [MnO_2(b) on the chart], only a 30% yield of retinene$_1$ was eluted. A second product was eluted with ether, which on further purification gave a 25% yield of a crystalline compound. From

* Part LI, *J.*, 1955, 2765.

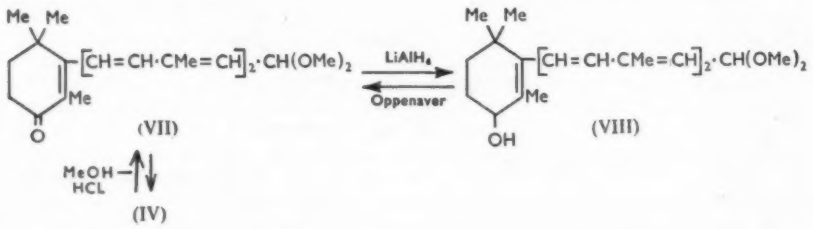
[1] Ball, Gordon, and Morton, *Biochem. J.*, 1948, **42**, 516.
[2] Farrer, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.
[3] Wald, *J. Gen. Physiol.*, 1947, **31**, 489.
[4] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[5] Wald, *J. Gen. Physiol.*, 1948, **31**, 489.
[6] Henbest, *J.*, 1951, 1074.

its physical properties and reactions this must be formulated as 3-oxoretinene$_1$ (IV). Similar treatment of retinene$_1$ also gave the 3-oxo-compound. As far as we are aware, oxidation of an allylic methylene group to an unsaturated ketone has not been effected previously by an insoluble reagent at room temperature, although the oxidation of *N*-methyl to *N*-formyl groups in mono- and di-methylanilines by the same manganese dioxide may be considered to be an analogous process.[7] The remarkable specificity of this oxidation occurring in the presence of the polyene chain prompted a preliminary examination of its generality.



Treatment of vitamin A_1 acetate (V) with a 20-fold weight of this manganese dioxide afforded some unchanged material and an acetoxy-ketone, which on hydrolysis gave 3-oxovitamin A_1 (VI) as golden plates ($\lambda_{max.}$ 3510 Å). This experiment proved therefore that a terminal carbonyl group in conjugation with the polyene system was not necessary to promote oxidation in the ring. However, an attempt to insert an oxo-group into anhydrovitamin A_1 was unsuccessful, the hydrocarbon being rapidly transformed into material displaying no characteristic ultraviolet absorption. β-Ionone is oxidised relatively slowly, the product apparently being 3-oxo-β-ionone. There are thus indications that in β-ionylidene compounds the rate of allylic oxidation by this type of manganese dioxide will parallel the rate of reaction of *N*-bromosuccinimide at the same position, *i.e.*, increasing rate with increasing unsaturation.

Not sufficient is as yet known about the course of reactions occurring by adsorption from solution on to the surface of an oxidising agent to warrant further discussion of the results obtained with the various batches of manganese dioxide. However, the fact that the material capable of oxidising an allylic methylene group to a ketone was prepared



under acidic conditions may be relevant for further work. Previous work [7] has shown that the oxidising power of manganese dioxide depends on the substrate. For the oxidations of retinene$_1$ and vitamin A_1 acetate to 3-oxo-compounds, approximately 9000 and 4600 g. of manganese dioxide are required respectively to give 16 g. of "available oxygen"—these figures may be compared with those given for the other oxidations in which the same commercial oxide was employed.

During this work it has also been shown that, in acidic methanol, retinene$_1$ and related compounds very readily form dimethyl acetals, from which the parent aldehydes are regenerated by acidic hydrolysis in aqueous acetone. The oxo-aldehyde (IV) affords an acetal (VII) in high yield, which on reduction by lithium aluminium hydride gives the hydroxy-acetal (VIII), converted by hydrolysis into 3-hydroxyretinene$_1$ (III), identical

[7] Henbest and Thomas, *J.*, 1957, 3032.

with that obtained by oxidation of vitamin A_1 by manganese dioxide. The hydroxyretinene (III) has also been prepared from retinene$_1$ by a modification of the route employed [6] to transform β-ionone into 3-hydroxy-β-ionone; the hydroxy-acetal (VIII) was an intermediate and could be oxidised by the Oppenauer method to the keto-acetal (VII) and thence converted into the keto-aldehyde (IV).

Light absorption of 3-substituted vitamin A_1 compounds

Compound	$\lambda_{max.}$ (Å)	ε
Vitamin A_1 (I)	3280	54,000
3-Oxovitamin A_1 (VI)	3510, 2780	34,000, 21,300
Retinene$_1$ (II)	3850	40,000
3-Hydroxyretinene$_1$ (III)	3750	40,000
3-Oxoretinene$_1$ (IV)	3800, 2930	42,500, 10,000
Retinene$_1$ dimethyl acetal	3280	47,000
3-Hydroxyretinene$_1$ dimethyl acetal (VIII)	3280	45,000
3-Oxoretinene$_1$ dimethyl acetal (VII)	3520, 2770	41,000, 22,000

The ultraviolet absorption characteristics of these 3-substituted vitamin A_1 compounds are listed in the accompanying Table. The three 3-oxo-compounds are characteristic in giving subsidiary maxima at shorter wavelengths.

Experimental

Formation of Retinene$_1$ (II) *and 3-Hydroxyretinene$_1$* (III).—A pentane solution (25 c.c.) of vitamin A_1 (prepared from vitamin A_1 acetate, 0·6 g.) was percolated through "precipitated" manganese dioxide (10 g.; B.D.H.). Washing with pentane (1 l.) afforded 80% of retinene$_1$. Further elution with ether–methanol (10 : 1) gave 3-hydroxyretinene$_1$ (0·1 g.) as a yellow oil, which was purified by further chromatography. Infrared spectrum on liquid: OH band at 3430 cm.$^{-1}$, C=O band at 1660 cm.$^{-1}$.

Repetition of this oxidation with manganese dioxide prepared by Haslam and Quibell's method (unpublished work at Manchester) gave an almost quantitative yield of retinene$_1$. In brief, this method involves treatment of a stirred solution of manganous sulphate tetrahydrate (200 g.) in water (200 c.c.) at 20° with potassium hydroxide solution (20 g. in 50 c.c. of water), followed immediately with potassium permanganate (130 g.) in water (2 l.). After 5 min. the solid was filtered off, and washed with water, and then sodium hydrogen carbonate solution until the pH of the washings was 5—7. The oxide was dried overnight at 100—120° in air. The average activity was $13·5 \times 10^{-4}$ g.-atoms of oxygen per g.

3 : 7-Dimethyl-9-(3-oxo-2 : 6 : 6-trimethylcyclohex-1-enyl)nona-2 : 4 : 6 : 8-tetraen-1-al (*3-Oxoretinene$_1$*) (IV) —A solution of vitamin A_1 (from vitamin A_1 acetate, 5 g.) in pentane (60 c.c.) was poured on manganese dioxide (100 g.; supplied by J. Woolley, Sons & Co. Ltd., and prepared by T. Tyrer & Co. Ltd., by addition of potassium permanganate solution to manganese sulphate solution followed by washing the product with water). Elution with pentane (3 l.) gave retinene$_1$ (1·13 g., 25%), and then further elution with ether afforded an orange oil (2 g.), which was rechromatographed on deactivated alumina (250 g.). The product from the main band crystallised from light petroleum–benzene (5 : 2) at −10°, to give *3-oxoretinene$_1$* (1·0 g.) as thick orange needles, m. p. 117—118° (Found: C, 81·0; H, 8·75. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%), C=O band at 1655 cm.$^{-1}$.

Retinene$_1$ (0·6 g.) in pentane (10 c.c.) was filtered through the same manganese dioxide (10 g.). Elution with pentane (700 c.c.) gave starting material (0·3 g.). Elution with ether provided crude 3-oxoretinene$_1$ (0·25 g.), which after purification as before had m. p. 116—117°.

3 : 7-Dimethyl-9-(3-oxo-2 : 6 : 6-trimethylcyclohex-1-enyl)nona-2 : 4 : 6 : 8 -tetraen-1-ol (*3-Oxovitamin A_1*) (VI).—Vitamin A_1 acetate (0·5 g.) in pentane (20 c.c.) was percolated through manganese dioxide (10 g.; Woolley). Starting material (0·21 g.) was recovered by elution with pentane (700 c.c.). Ether eluted a product which was chromatographed on deactivated alumina (100 g.). The main yellow band gave material which was heated in methanol (10 c.c.) containing potassium hydroxide (100 mg.) for 45 min. The product (isolated with ether), dissolved in ether–pentane (1 : 1) was cooled to −10°; the *3-oxovitamin A_1* (90 mg.) crystallised as orange-yellow

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cubes, m. p. 140—141° (Found: C, 79·55; H, 9·25. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), having an OH band at 3400 and a C=O band at 1655 cm.$^{-1}$.

Alternatively, a pentane solution (50 c.c.) of vitamin A_1 acetate (1 g.) and manganese dioxide (20 g.; Woolley) was rolled for 20 hr. Chromatography gave starting material (0·27 g.), and pure oxo-acetate (0·20 g.), which did not crystallise but gave a good yield of solid oxo-vitamin on hydrolysis. If the proportion of manganese dioxide was doubled only a trace of starting material was obtained but the yield of oxo-acetate was not substantially improved. Manganese dioxide (Haslam and Quibell) did not oxidise vitamin A_1 acetate.

Conversion of Retinene$_1$ into 3-Oxoretinene$_1$ by N-Bromosuccinimide.—Pure, finely powdered *N*-bromosuccinimide (0·5 g.) was added at 0° to a solution of retinene$_1$ (0·64 g.) in freshly purified chloroform (20 c.c.), and the mixture stirred vigorously in air for 20 min. Light petroleum (40 c.c.) was added to the brown solution, and the mixture filtered into a solution of sodium formate (1·25 g.) in 90% formic acid (15 c.c.). After evaporation under reduced pressure to remove the light petroleum and most of the chloroform, dioxan (30 c.c.) was added and the mixture stirred at 20° for 2 hr. The formyloxy-aldehyde ($\lambda_{max.}$ 3710 Å) was isolated with ether, and dissolved in methanol (20 c.c.), and treated with concentrated hydrochloric acid (0·1 c.c.), the dimethyl acetal being formed ($\lambda_{max.}$ 3270 Å, see below). Hydrolysis of this with potassium hydroxide (0·55 g.) in 80% methanol (20 c.c.), followed by isolation and chromatography, afforded 3-hydroxyretinene$_1$ dimethyl acetal (0·2 g.) (see below). This was dissolved in dry benzene (3 c.c.), added to a solution of aluminium *tert.*-butoxide (0·24 g.) in dry benzene (4 c.c.) and acetone (1 c.c.), and heated for 24 hr. After isolation with ether, the acetal was hydrolysed with hydrochloric acid (0·01 c.c.) in acetone (5 c.c.), and the crude product purified by chromatography and crystallisation to give pure oxoretinene$_1$ (30 mg.), m. p. and mixed m. p. 116—117°.

Retinene$_1$ Dimethyl Acetal and 3-Oxoretinene$_1$ Dimethyl Acetal (VII).—Concentrated hydrochloric acid (0·1 c.c.) was added to retinene$_1$ (0·5 g.) dissolved in methanol (50 c.c.). After 10 min. the acid was neutralised by addition of triethanolamine (0·2 g.) in methanol (2 c.c.), and the product isolated with ether and purified by chromatography. The *acetal* (0·5 g.) was obtained as a pale yellow oil (Found: C, 80·5; H, 9·9. $C_{22}H_{34}O_2$ requires C, 80·0; H, 10·35%). C–O bands at 1055 and 1130 cm.$^{-1}$.

Similar treatment of 3-oxoretinene$_1$ (0·175 g.) gave the monoacetal (0·14 g.) as a yellow oil, with C=O band at 1660 cm.$^{-1}$ and C–O bands at 1060 and 1130 cm.$^{-1}$.

3-Hydroxyretinene$_1$ from 3-Oxoretinene$_1$.—A solution of lithium aluminium hydride (30 mg.) in dry ether (10 c.c.) was added with shaking to a solution of 3-oxoretinene$_1$ dimethyl acetal (0·14 g.) in dry ether at −30°. After 40 min. at −30° the solution was treated with ethyl acetate, and the product isolated as usual. The acetal (0·11 g.) was a pale yellow oil, having C–O bands at 1055 and 1130 cm.$^{-1}$. Hydrolysis of the acetal was effected by dissolving it in acetone (5 c.c.) containing concentrated hydrochloric acid (0·02 c.c.). Water was added after 5 min., and after chromatography 3-hydroxyretinene$_1$ was obtained as a yellow oil (0·1 g.), whose ultraviolet and infrared absorptions were identical with those of the product from manganese dioxide oxidation of vitamin A_1.

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986. *The Chemistry of Fungi. Part XXVIII.* Sclerotiorin and its Hydrogenation Products.*

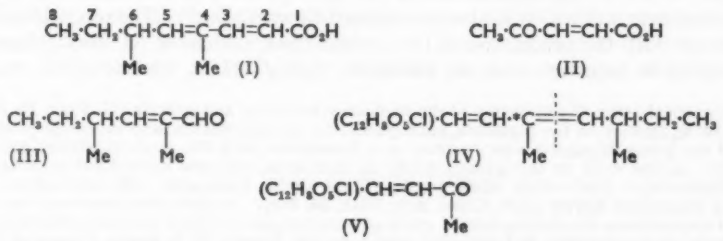
By R. A. Eade, H. Page, Alexander Robertson, K. Turner, and W. B. Whalley.

Degradation of the yellow, chlorine-containing pigment sclerotiorin, $C_{21}H_{23}O_5Cl$, from *Penicillium sclerotiorum* van Beyma, with alkali gives hydrochloric acid, formic acid, and 4 : 6-dimethylocta-*trans*-2 : 4-dienoic acid (I). With ammonia and primary amines sclerotiorin reacts to give amino-compounds of the general formula $C_{21}H_{23}O_4NCl{\cdot}R$; the nature of this reaction is discussed.

Hydrogenation of sclerotiorin gives tetrahydrosclerotiorin, $C_{21}H_{27}O_5Cl$, by the saturation of the diene side chain, whilst reduction with hydriodic acid forms dihydrosclerotiorin, $C_{21}H_{25}O_5Cl$, by the saturation of the double bond in the side chain adjacent to the sclerotiorin nucleus. Prolonged hydrogenation of sclerotiorin or dihydro- or tetrahydro-sclerotiorin yields two phenols, sclerotinol, $C_{19}H_{29}O_3Cl$, and sclerotol, $C_{19}H_{27}O_3Cl$, the constitutions of which are discussed.

From *P. sclerotiorum* van Beyma a second analogous colouring matter, rotiorin, has been isolated.

First isolated from the mycelium of *Penicillium sclerotiorum* van Beyma by Reilly and Curtin,[1,2] who proposed the empirical formula $C_{20}H_{19}O_5Cl$ or $C_{20}H_{21}O_5Cl$, the yellow chlorine-containing metabolite sclerotiorin was examined by Watanabe[3] who also obtained the compound from *P. multicolor* Grigorieva Manoilova and Poradielova and suggested the formula, $C_{21}H_{23}O_5Cl$. Since methylation and acetylation experiments were unsuccessful this author concluded that the pigment was devoid of a hydroxyl group and, from its failure to liberate iodine from acidified potassium iodide solution and its inertness towards sodium hydrogen sulphite, inferred that it did not contain a quinonoid system. On oxidation with chromic oxide sclerotiorin gave a yellow compound, $C_{16}H_{13}O_6Cl$, together with α-methylbutyric acid, whilst degradation with alkali furnished formic acid and a crystalline, optically active, unsaturated acid, $C_{10}H_{16}O_2$, which was reduced catalytically to the optically active saturated acid, $C_{10}H_{20}O_2$, characterised as the *p*-bromophenacyl derivative. From these results and the application of Woodward's rules[4] to its ultraviolet absorption spectrum, Watanabe[3] suggested that the acid, $C_{10}H_{16}O_2$, was 4 : 6-dimethylocta-2 : 4-dienoic acid (I).



About the same time Birkinshaw[5] also reported the isolation of sclerotiorin from the same organisms and described preliminary experiments on the metabolite for which he

* Part XXVII, *J.*, 1957, 3497.

[1] Reilly and Curtin, *Biochem. J.*, 1940, **34**, 1419.
[2] *Idem, ibid.*, 1943, **37**, 36.
[3] Watanabe, *J. Pharm. Soc. Japan*, 1952, **72**, 807.
[4] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76.
[5] Birkinshaw, *Biochem. J.*, 1952, **52**, 283.

proposed the empirical formula, $C_{21}H_{23}O_5Cl$, but considered that the alternative formula, $C_{21}H_{25}O_5Cl$, was not entirely excluded. Birkinshaw confirmed the formation of the acid, $C_{10}H_{16}O_2$, established the relative position of the two double bonds by the preparation of a maleic anhydride adduct, and concluded that it had the constitution (I) since ozonolysis furnished (+)-α-methylbutyraldehyde along with β-acetylacrylic acid (II). The presence of an aldehydic or ketonic carbonyl group in sclerotiorin was inferred from the production of a dark red derivative, $C_{27}H_{27(29)}O_8N_4Cl$ with 2 : 4-dinitrophenylhydrazine, a red derivative, $C_{21}H_{23(25)}O_4N_2Cl$, with hydroxylamine, and a red product, $C_{21}H_{24(26)}O_4NCl$, with aqueous ammonia.

In an independent investigation * initiated in these laboratories in 1950, sclerotiorin was isolated from *P. sclerotiorum* and *P. multicolor*, and from its analytical results together with those of numerous derivatives and degradation products the metabolite clearly appeared to have the empirical formula $C_{21}H_{23}O_5Cl$; along with sclerotiorin from the mycelium of *P. sclerotiorum* there was obtained a second pigment, rotiorin, $C_{23(22)}H_{24(22)}O_5$, the chemistry of which will be described in a subsequent memoir. In preliminary work it was found that sclerotiorin is optically active, and from its infrared absorption spectrum and its failure to be acetylated or methylated under the usual conditions, appeared to be devoid of hydroxyl groups, a view which was substantiated by the negative Zerewitinoff estimation. With diazomethane it furnished an intractable gum and with methyl iodide or methyl sulphate and potassium carbonate intractable brown solids; the metabolite is unstable even in the mild alkaline conditions of the acetone–potassium carbonate methylation. Though the behaviour of sclerotiorin with aqueous-alcoholic sodium hydroxide is characteristic of a lactone clear evidence supporting the presence of this system is absent owing, in the main, to the complex behaviour of the compound; in attempts to detect a lactone system application of the standard methylation procedure [6] resulted either in unchanged sclerotiorin or in complete degradation.

Although sclerotiorin is moderately stable towards cold or hot dilute mineral acids and is unchanged by hydrogen chloride in ethyl acetate it is very sensitive to alkali (cf. Watanabe [3] and Birkinshaw [5]). Degradation with aqueous sodium hydrogen carbonate or preferably with dilute aqueous sodium hydroxide (cf. Watanabe [3]) readily gives hydrochloric acid, formic acid, the conjugated dienoic acid, $C_{10}H_{16}O_2$, which is clearly 4 : 6-dimethylocta-2 : 4-dienoic acid (I), and 2 : 4-dimethylhex-2-enaldehyde (III). The ultraviolet absorption spectrum of the dienoic acid indicates the conjugation of the diene system and of this system with the carboxyl group,[8,9] whilst infrared absorption at 988 cm.$^{-1}$ (m) indicates the *trans*-arrangement of the αβ-disubstituted double bond (cf. Crombie *et al.*[10]). Hydrogenation of the acid yields (+)-4 : 6-dimethyl-*n*-octanoic acid, the constitution of which has been confirmed by synthesis.[10] The physical properties in conjunction with the production of (+)-α-methylbutyraldehyde (cf. Birkinshaw [5]) and of pyruvaldehyde together with an aldehyde, $C_8H_{14}O$ (III), by ozonolysis served to

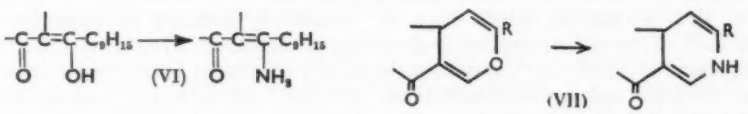
* Simultaneously with the initiation of the work on sclerotiorin and rotiorin (H. Page, Ph.D. thesis, Liverpool, 1953), studies on the pigments, rubropunctatin, monascorubrin, and monascin produced by members of the genus *Monascus* were resumed in collaboration with Dr. A. D. G. Powell (late of this Department); earlier work on this group, chiefly on monascin, had been carried out in collaboration with Dr. Richmond in 1937—1939 whose results (Ph.D. thesis, Liverpool, 1940) covered the ground described by Geiger and Karrer (*Helv. Chim. Acta*, 1941, **24**, 289). As indicated elsewhere,[7] sclerotiorin and rotiorin are members of a closely related group of fungal pigments which have been shown to include rubropunctatin, monascorubrin, and (possibly) monascin (Dr. Powell, Ph.D. thesis, Liverpool, 1954).

In an earlier communication [7] the generic name azaphilone was applied to this group of substances. Although this has certain advantages it is now clear that the general application must remain in abeyance until the nature of the compounds has been more clearly defined. A.R.

[6] Canter and Robertson, *J.*, 1931, 1875.
[7] Powell, Robertson, and Whalley, *Chem. Soc. Special Publ.*, 1957, No. 5, p. 27.
[8] Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones and Enzymes," Hilger, London, 2nd edn., 1942, p. 19.
[9] Crossley and Hilditch, *J.*, 1949, 3353.
[10] Crombie, Manzoor-i-Khuda, and Smith, *J.*, 1957. 479.

establish the detailed structure of the dienoic acid. The structure of 2 : 4-dimethylhex-2-enaldehyde (III) is in agreement with the bright red colour of the 2 : 4-dinitrophenylhydrazone, which is indicative of αβ-unsaturation, whilst the ultraviolet absorption spectrum of the semicarbazone [$\lambda_{max.}$ 262 mμ (ε 32,400)] lies within the range [$\lambda_{max.}$ 267 ± 7·5 mμ (ε 10,000—35,000)] characteristic of the C:C·CH:N·NH·CO·NH_2 grouping.[11] Ozonolysis of sclerotiorin furnished the aldehyde (III) whilst scission of the side chain in sclerotiorin with ozone, as indicated at the broken line in the partial formula (IV), gave rise to (+)-α-methylbutyraldehyde and a ketone, pentanorsclerotiorone $C_{16}H_{13}O_6Cl$, which contains the sclerotiorin nucleus intact and appears to be identical with the product obtained in low yield by Watanabe [3] on oxidation of sclerotiorin with chromic oxide. Formulation of this oxidation product as the methyl ketone (V) is in accordance with, *inter alia*, the structure of the side chain of sclerotiorin, the failure of the product to form a dimedone derivative, and the ready production of iodoform whereas sclerotiorin does not undergo the haloform reaction. In agreement with structure (V) the conjugation of the newly introduced carbonyl group is indicated by the appearance of an additional band in the infrared absorption spectrum at 1698 $cm.^{-1}$ (m). Further, the optical activity of this ketone, from which the asymmetric carbon atom present in the side chain has been removed, indicates that the sclerotiorin kernel possesses at least one source of optical activity.

Despite the orange colour, sclerotiorin does not exhibit the usual quinonoid reactions (cf. Watanabe [3]), and is, for example, inert towards sulphur dioxide and bisulphites whilst catalytic reduction initially saturates the side chain with the formation of a tetrahydro-derivative in which the nucleus remains intact (see below). Although reductive acetylation of sclerotiorin led to a deep-seated degradation with the formation of an extremely difficultly separable, complex mixture, the deepening of colour on dissolution in alcoholic alkali indicates a partial or pseudo-quinonoid system. Attempts to confirm this by the formation of an anilinoquinone on treatment with aniline resulted in the production of a red derivative, *N*-phenylsclerotioramine, $C_{27}H_{28}O_4NCl$, in which one oxygen atom of sclerotiorin has been replaced by the PhN residue and which did not have the expected properties of an anilinoquinone. Similarly, with methylamine sclerotiorin readily furnished *N*-methylsclerotioramine, $C_{22}H_{26}O_4NCl$, and with hydrazine a deep purple *N*-aminosclerotioramine, $C_{21}H_{24}O_4NCl$ (cf. Birkinshaw [5]). The close similarity between the infrared absorption spectra of sclerotiorin and sclerotioramine indicates that the reaction with primary amines is probably not accompanied by a deep-seated change; the spectra may be regarded as compatible with the change $-O- \longrightarrow -NH-$. Further, the production of 2 : 4-dimethylhex-2-enaldehyde by ozonolysis of sclerotioramine shows that the aliphatic side chain is not concerned in the formation of sclerotioramine. From their general properties it appears that these substances are of the enamine type and may well be produced from a β-diketo-, β-aldehydo-, or keto-ester system (VI) or its cyclic equivalent (VII). Since the degradation of sclerotioramine, which occurs with both acid



and alkali, does not give ammonia, formic acid, or 4 : 6-dimethylocta-2 : 4-dienoic acid (I) it seems highly probable that the nitrogen atom of the amino-compounds is contained in a heterocyclic system involving the acid residue (I) and the formyl moiety as in (VII). The formation of the amino-compounds from ammonia and primary amines only and the failure of secondary or tertiary amines to react support this concept which implies the necessity of the group $-NH_2$ in the reacting amine. In agreement with a structure of the

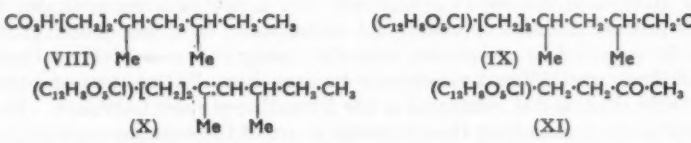
[11] Evans and Gillam, *J.*, 1943, 565.

kind (VII) the infrared spectrum of sclerotioramine exhibits absorption in the :NH stretching region at 3205 (m) and 3058 cm.$^{-1}$ (s), whilst in *N*-methylsclerotioramine absorption is absent in this region, thus showing that the nitrogen atom is tertiary.

In contrast to the other analogous products, *N*-phenylsclerotioramine is formed by way of a comparatively stable, intermediate, yellow adduct, $C_{27}H_{30}O_5NCl$, which is more readily soluble in aqueous solutions than the parent compound or *N*-phenylsclerotioramine, does not exhibit hydroxyl group absorption in the infrared spectrum, and is converted into the phenylamino-compound by hydrogen ions but much more readily by hydroxyl ions. This behaviour in conjunction with the intensification of colour observed in the formation of the amino-compounds supports the concept that the products are enamines where the intermediate adduct of aniline and sclerotiorin is of a salt-like nature (cf. Cromwell [12]).

Sclerotioramine is also a natural product since it has been isolated, together with sclerotiorin, from the mycelium of *P. multicolor* grown under special conditions.

Tetrahydrosclerotiorin, $C_{21}H_{27}O_5Cl$, which is readily formed by catalytic hydrogenation, along with a mixture of intractable degradation products, gave, on oxidation with chromic oxide, 4 : 6-dimethyl-*n*-octanoic acid (VIII), thereby showing that the hydrogenation of sclerotiorin to tetrahydrosclerotiorin is confined to the saturation of the side chain. Since this reaction involves the production of a new asymmetric centre at the C-atom* in formula (IV), tetrahydrosclerotiorin (IX) is a mixture of two diastereoisomerides, m. p. 142—144°, of which one only was originally obtained pure. Subsequently, by a prolonged fractional crystallisation this mixture has been resolved to give α-tetrahydro-, m. p. 118°, and β-tetrahydro-sclerotiorin, m. p. 159°. For present degradation experiments the mixture, m. p. 142—144°, was employed but it seems likely from the separation results that the β-diastereoisomeride greatly predominates in the mixture. For the same reason all tetrahydrosclerotiorin derivatives and degradation products retaining the hydrogenated side-chain intact may be expected to be mixtures of two diastereoisomerides; this applies, *e.g.*, to sclerotinol and sclerotol described below. Though Watanabe [3] reported the preparation of a substance, m. p. 130—132°, in low yield, believed to be hexahydrosclerotiorin no evidence for the existence of this derivative has been obtained in the present work, and it appears likely that the product was impure tetrahydrosclerotiorin.



Tetrahydrosclerotiorin shows infrared absorption at 1748 (s), 1727 (m), 1647 (vs), 1590 (m), and 1536 (m) cm.$^{-1}$. It has been found that all the derivatives of sclerotiorin which retain the sclerotiorin nucleus have a peak close to 773 cm.$^{-1}$ (s—m) (unpublished work in this laboratory) which may be tentatively ascribed to aliphatic chlorine absorption.[13] Thus any absorption peak arising in these derivatives at or close to double this frequency, *i.e.*, 1536 cm.$^{-1}$, may be provisionally attributed to the first overtone of the chlorine vibration and not to double-bond vibration. Hence if the peak at 1536 cm.$^{-1}$ exhibited by tetrahydrosclerotiorin is assigned to this overtone stretching frequency there remain four peaks attributable to double bonds. The peaks at 1748 and 1727 cm.$^{-1}$ may, with reasonable certainty, be assigned to the C=O stretching and, since sclerotiorin does not appear to contain an aromatic residue, the peaks at 1590 and 1647 cm.$^{-1}$ may be ascribed to a double bond conjugated with a carbonyl group.[14]

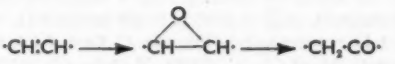
Reduction of sclerotiorin under carefully controlled conditions with hydriodic acid gave

[12] Cromwell, *Chem. Rev.*, 1946, **38**, 83.
[13] Bellamy, "Infra-Red Spectra of Complex Molecules," Methuen, London, 1954, p. 271.
[14] Ref. 13, p. 117.

dihydrosclerotiorin, whose partial structure (X) was readily established by ozonolysis to (+)-α-methylbutyraldehyde and the methyl ketone, pentanordihydrosclerotiorone, $C_{16}H_{15}O_6Cl$ (XI).

On prolonged catalytic hydrogenation with a palladium–charcoal catalyst in acetic acid sclerotiorin, or dihydro- or tetrahydro-sclerotiorin, undergoes a complex change with the elimination of two carbon atoms and the formation of two optically active phenolic products, sclerotinol, $C_{19}H_{29}O_3Cl$, and sclerotol, $C_{19}H_{27}O_3Cl$, in comparatively poor yields; reduction in alcohol or acetic acid with a platinum catalyst gave only sclerotinol, in low yield, accompanied by much intractable gum. Of these two, the main product is sclerotinol, a dihydric phenol forming a diacetate, a dimethyl ether, and a di-*p*-nitrobenzoate. The third oxygen atom in sclerotinol is present in a carbonyl group which readily forms derivatives and, from the ultraviolet absorption spectrum and the infrared absorption at 1712 cm.$^{-1}$ (s), together with the pale yellow colour of the 2 : 4-dinitrophenylhydrazone, is clearly an aliphatic unconjugated carbonyl residue. Further, the resistance of di-*O*-acetyl- and di-*O*-methyl-sclerotinol to oxidation, in conjunction with the infrared spectral data, indicates that this carbonyl group is ketonic and not aldehydic. Since it has a negative ferric reaction in alcohol and cannot be oxidised to a quinone, sclerotinol appears to be a resorcinol and not a catechol or quinol derivative. Moreover, because the saturated alkyl residue equivalent to the acid (VIII) is present, sclerotinol can contain only one benzenoid ring. Because this phenol does not couple with benzenediazonium chloride or give a fluorescein reaction with phthalic acid or anhydride it is probable that the benzenoid system is substituted in the *o*- and *p*-position to the hydroxyl groups although steric effects on the coupling reaction cannot be excluded entirely; it seems likely that the aromatic system is fully substituted. The molecular rotation indicates that the optical activity of sclerotinol is associated only with the asymmetric carbon atom of the alkyl residue and, although experimental proof has not yet been possible, the compound may well be, for the reasons which apply to tetrahydrosclerotiorin, a mixture of two diastereoisomerides; this applies also to sclerotol. The chlorine atom of sclerotinol cannot be removed by catalytic hydrogenation with Raney nickel or palladium–barium carbonate or by the action of Raney nickel in boiling alcohol. Di-*O*-methylsclerotinol is unaffected by the same reagents, by boiling alcoholic alkali with or without Raney nickel, or by alcoholic silver acetate. These observations indicate that the halogen in this phenol is aromatic and not aliphatic.

On reduction with lithium aluminium hydride sclerotinol gave a secondary alcohol. Similarly formed from the di-*O*-methyl ether, the secondary alcohol $C_{19}H_{29}OCl(OMe)_2$, which exhibited strong infrared hydroxylic absorption at 3676 cm.$^{-1}$ in place of the carbonyl absorption of the parent ether, gave on dehydration the ethenoid derivative $C_{19}H_{27}Cl(OMe)_2$, the light absorption of which indicates that the double bond is conjugated with the aromatic nucleus. Attempts to hydroxylate the olefin with osmium tetroxide were unsuccessful and, unexpectedly, ozonolysis regenerated the parent ketone in high yield, a reaction which may proceed thus:



in accordance with the conversion of amyrin acetate into 3β-acetoxy-13*a*-ursan-12-one [15] and similar to the oxidation of, *e.g.*, 2-methylbut-2-ene to 3-methylbutan-2-one [16] with chromic acid. Interaction of di-*O*-methylsclerotinol and methylmagnesium iodide gave a tertiary alcohol, $C_{22}H_{37}O_3Cl$, which exhibited infrared hydroxyl absorption at 3670 cm.$^{-1}$ (s) but not carbonyl absorption. Phenylmagnesium bromide afforded an analogous tertiary alcohol, but neither alcohol could be satisfactorily dehydrated or oxidised.

[15] Allan, Spring, and Stevenson, *J.*, 1955, 3072.
[16] Hickinbottom, Peters, and Wood, *J.*, 1955, 1360.

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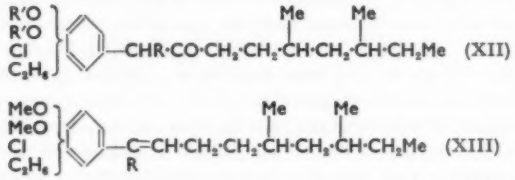
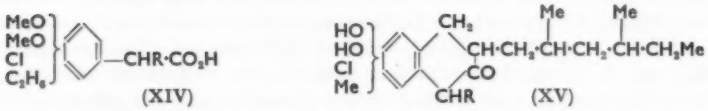
Since the carbonyl group of sclerotinol, which is not conjugated with the nucleus, in all probability appears as the carboxyl of the dienoic acid (I) it seems likely that sclerotinol and its dimethyl ether contain the systems (XII; R′ = H) and (XII; R′ = Me) respectively and hence the olefin may be formulated as (XIII). If a benzyl ketone residue is





present it seems likely that this does not carry a phenolic hydroxyl in the *o*-position because attempts to convert sclerotinol into a benzofuran derivative by standard methods were unsuccessful. It is not clear whether R is hydrogen or a methyl residue. In attempts to decide this, the oxime of di-*O*-methylsclerotinol was subjected to the Beckmann reaction, giving a product, $C_{21}H_{34}O_3NCl$, with the expected absorption at **1642**, **1553**, and **3279** cm.$^{-1}$, but as it could not be hydrolysed under fairly drastic conditions or reduced with lithium aluminium hydride this substance may not be the expected amide. That the carbonyl system in sclerotinol is not contained in a cyclic system follows from the fact that, although it has not so far been possible to oxidise di-*O*-methylsclerotinol satisfactorily, the corresponding diacetate gave a small yield of a monobasic acid (XIV), having the properties of a phenylacetic acid. The isolation of a phenylacetic acid and not a benzoic acid is in keeping with the observed resistance of highly hindered phenylacetic acids to further oxidation.[17]

Sclerotol, which closely resembles sclerotinol and has almost identical ultraviolet and infrared absorption spectra, contains two *meta*-phenolic hydroxyl groups, and forms a dimethyl ether $C_{19}H_{25}OCl(OMe)_2$. As in sclerotinol the carbonyl group is not conjugated with the aromatic system. Sclerotol, however, possesses two hydrogen atoms less than sclerotinol and may have a structure of β-tetralone type (XV).

Experimental

Sclerotiorin.—This was obtained from *Penicillium sclerotiorum* van Beyma and *P. multicolor* Grigorieva-Manoilova and Poradielova grown on a modified Czapek–Dox medium as described by Curtin and Reilly.[1,2] Extraction of the dried milled mycelium (3 kg.) from *P. sclerotiorum* van Beyma with light petroleum (b. p. 60—80°) furnished the crude compound which was purified from methanol, giving the metabolite (200—250 g.) in orange-yellow needles, m. p. 206°, unchanged on sublimation at 170°/0·01 mm., giving a negative ferric and iodoform reaction (cf. Watanabe [3] and Birkinshaw [5]), $[\alpha]_D^{20}$ +493° (*c* 0·298 in EtOH), $\lambda_{max.}$ 224, 287, 365, 449 mμ (log ε 4·06, 4·11, 4·50, and 4·11 respectively) (Found: C, 64·4, 64·5, 64·3, 64·2; H, 6·1, 5·7, 6·1, 5·9; Cl, 8·7, 9·1. Calc. for $C_{21}H_{23}O_5Cl$: C, 64·5; H, 5·9; Cl, 9·1%). Sclerotiorin is readily soluble in alcohol, methanol, ethyl acetate, or benzene, sparingly soluble in light petroleum (b. p. 60—80°) or ether. Though insoluble in cold 2N-aqueous sodium hydroxide, the compound dissolves very slowly on prolonged contact with this reagent but is not extracted from an ethereal solution by it. It readily dissolves in aqueous-alcoholic 2N-sodium hydroxide, forming a deep purple-red solution from which it is not precipitated on dilution with water but is recovered unchanged upon immediate acidification.

Percolation, with ether, of the residues left from the light petroleum extract, followed by concentration of the liquor, gave a semicrystalline solid which was purified from methanol, to

[17] Lloyd and Whalley, *J.*, 1956, 3209.

furnish *rotiorin* in red needles (*ca.* 8 g.), m. p. 246° (decomp.) (Found: C, 72·6, 72·4, 72·4, 72·7; H, 6·8, 6·2, 6·3, 6·5%; OMe, 0; *M*, 366. $C_{23}H_{24}O_5$ requires C, 72·6; H, 6·4%; *M*, 380).

From the dried, powdered, mycelium (3·5 kg.) of *P. multicolor*, which did not seem to contain rotiorin, sclerotiorin (600—700 g.) was extracted directly with ether. On one occasion *P. multicolor* G.-M.P. was grown on the normal modified Czapek–Dox medium for five weeks at 20—30° and on extraction the dried mycelium gave sclerotiorin contaminated with an orange-red impurity which was concentrated by removing the greater part of the sclerotiorin with hot light petroleum (b. p. 60—80°). The red residue was then purified by chromatography on neutralised aluminium oxide from benzene. Sclerotiorin was rapidly eluted by benzene, followed, more slowly, by a red band, which furnished sclerotioramine in red needles, m. p. and mixed m. p. 235° (decomp.), having an infrared spectrum identical with that of a specimen prepared from sclerotiorin.

60—80% of the starting material was recovered when sclerotiorin was treated with boiling acetic anhydride–sodium acetate, acetic anhydride–sulphuric acid at 100° (5 min.), or acetic anhydride–pyridine at 100° (1 hr.).

Degradation of Sclerotiorin with Alkali.—(*a*) Sclerotiorin (2 g.) was heated with boiling 5% aqueous potassium hydroxide (100 ml.) for 5 min., the dark brown filtered solution was acidified with 2N-sulphuric acid, and a solution of the brown amorphous precipitate in ether was washed with 2N-aqueous sodium hydrogen carbonate and then 2N-aqueous sodium hydroxide. Acidification of the former extract gave 4 : 6-dimethylocta-2 : 4-dienoic acid which separated from light petroleum (b. p. 60—80°) in prisms (0·8 g.), m. p. 92°, $[\alpha]_D^{20}$ +64·4° (*c* 2·12 in EtOH), $\lambda_{max.}$ 261 mμ (log ε 4·433) (Watanabe [3] records $[\alpha]_D^{22}$ +68·7° in EtOH) (Found: C, 71·5; H, 9·4%; equiv., 170. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·6%; equiv., 168). Hydrogenation of this acid (2 g.) in alcohol (50 ml.) with platinic oxide (0·1 g.) was complete in 30 min., giving the 4 : 6-dimethyl-*n*-octanoic acid, b. p. 98°/1 mm., $[\alpha]_D^{20}$ +19·4° (*c* 2·38 in EtOH), $[M]_D^{20}$ +2336° (Found: C, 69·9; H, 11·6. Calc. for $C_{10}H_{20}O_2$: C, 69·7; H, 11·7%). Acidification of the aqueous sodium hydroxide extract furnished an intractable solid.

The combined filtrates from five degradation experiments were distilled with steam until the distillate was neutral. This distillate, which contained chloride ions, was neutralised with 0·1N-aqueous sodium hydroxide and evaporated to dryness, leaving the colourless mixed sodium salts (1·7 g.), a portion of which, on treatment with *o*-phenylenediamine, gave benziminazole (from formic acid), m. p. and mixed m. p. 169°; this furnished a picrate, m. p. and mixed m. p. 225°. These compounds depressed the m. p. of 2-methylbenziminazole and its picrate respectively.

The same results were obtained when the degradation was carried out with zinc dust and 5% aqueous potassium hydroxide.

(*b*) A mixture of sclerotiorin (5 g.) and 10% aqueous sodium hydroxide (200 ml.) was slowly distilled, with the addition of sufficient distilled water to maintain the volume, until a test portion of the distillate no longer gave a precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate. Treatment of the distillate with an excess of this reagent precipitated 2 : 4-*dimethylhex-2-enaldehyde* 2 : 4-*dinitrophenylhydrazone* (0·3 g.) which separated from methanol in red needles, m. p. 159° (Found: C, 55·3; H, 6·2; N, 18·1. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%). The presence of other 2 : 4-dinitrophenylhydrazones in the crude product could not be detected and acidification of the alkaline hydrolysate furnished 4 : 6-dimethylocta-2 : 4-dienoic acid (1 g.).

Repetition of this experiment, but with addition of a saturated solution of sodium acetate (4·5 g.) and semicarbazide hydrochloride (1 g.) to the concentrated distillate (30 ml.), gave 2 : 4-*dimethylhex-2-enaldehyde semicarbazone* which separated from light petroleum (40—60°) in needles, m. p. 149°, $[\alpha]_D^{20}$ +72° (*c* 0·83 in EtOH), $\lambda_{max.}$ 262 mμ (log ε 4·51) (Found: C, 59·3; H, 9·2; N, 23·1. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·4; N, 22·9%).

(*c*) Degradation of sclerotiorin (1 g.) with boiling 2N-aqueous sodium hydrogen carbonate (40 ml.) for 3 hr. as in method (*b*) furnished a distillate (50 ml.) from which 2 : 4-dimethylhex-2-enaldehyde was isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159°. Other aldehydic or ketonic substances were not detected.

Ozonolysis of 4 : 6-*Dimethylocta-2* : 4-*dienoic Acid.*—A mixture of ozone and oxygen was passed through a solution of this acid (0·9 g.) in ethyl acetate (90 ml.) at room temperature for 30 min. and, after the removal of the solvent in a vacuum, the gummy residue was treated with an excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. One hour later the mixture of

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semicrystalline products (1·8 g.) was collected, triturated with 2N-aqueous sodium hydrogen carbonate, washed with hot alcohol, and purified from dioxan, giving pyruvaldehyde bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 300° (decomp.) (Found: N, 25·6. Calc. for $C_{15}H_{12}O_8N_8$: N, 25·9%). Concentration of the alcoholic washings gave 2 : 4-dimethylhex-2-enaldehyde 2 : 4-dinitrophenylhydrazone (0·2 g.), m. p. and mixed m. p. 159°.

When the time of ozonolysis was extended to 2 hr. the product consisted of the bis-2 : 4-dinitrophenylhydrazone of pyruvaldehyde together with (+)-α-methylbutyraldehyde 2 : 4-dinitrophenylhydrazone which was isolated from the alcoholic washings of the crude product as plates (0·2 g.), m. p. 122—124°. Purified by chromatography from benzene–light petroleum (b. p. 60—80°) (1 : 1) on aluminium oxide this had m. p. 132°, $[\alpha]_D^{20}$ +29·8° (*c* 1·37 in ethyl acetate) (Badin and Pacsu [18] give m. p. 132—133°, $[\alpha]_D^{20}$ +31·2° in acetone) (Found: C, 49·9; H, 5·3; N, 20·7. Calc. for $C_{11}H_{14}O_4N_4$: C, 49·6; H, 5·3; N, 21·0%). The infrared absorption was identical with that of the 2 : 4-dinitrophenylhydrazone of (±)-α-methylbutyraldehyde.

Ozonolysis of Sclerotiorin.—A stream of ozone and oxygen was passed into a solution of sclerotiorin (0·5 g.) in ethyl acetate (50 ml.) at room temperature for 1 hr. and the residue left on removal of the solvent in a vacuum was treated with water (250 ml.) and barium carbonate (2 g.). 12 Hr. later the aqueous solution was decanted from an orange solid and distilled into an excess of 2 : 4-dinitrophenylhydrazine sulphate, giving a precipitate which on purification by chromatography furnished 2 : 4-dimethylhex-2-enaldehyde 2 : 4-dinitrophenylhydrazone (50 mg.), m. p. and mixed m. p. 159°.

Ozonolysis of sclerotiorin (2 g.), in ethyl acetate (100 ml.), at room temperature for 1·75 hr. with subsequent decomposition of the ozonide with water (100 ml.) for 12 hr. and distillation of the aqueous solution gave the 2 : 4-dihydrophenylhydrazone of (+)-α-methylbutyraldehyde (0·4 g.) in yellow plates, m. p. and mixed m. p. 132°.

The dried orange solid obtained from the ozonide was purified from alcohol, giving a ketone, pentanorsclerotiorone, in stout, orange needles (0·5—0·8 g.), m. p. 234° (decomp.) with darkening from *ca.* 222°, $[\alpha]_D^{20}$ +381° (*c* 0·91 in $CHCl_3$), $\lambda_{max.}$ 243, 281, 311, 355, and 426 mμ (log ε 4·04, 4·25, 4·08, 4·23, and 3·84 respectively), identical with the product formed in much lower yield by the oxidation of sclerotiorin with chromium trioxide [Watanabe [3] gives m. p. 233—235° (decomp.)] (Found: C, 57·2; H, 4·1; Cl, 10·2. Calc. for $C_{16}H_{13}O_6Cl$: C, 57·1; H, 3·9; Cl, 10·6%). This ketone, which readily furnished iodoform under standard conditions, is sparingly soluble in alcohol, benzene, or acetic acid, insoluble in ether or light petroleum (b. p. 60—80°), and readily soluble in cold 2N-aqueous sodium hydroxide. The alcoholic solution, which has a negative ferric reaction, becomes an intense purple-red on the addition of 2N-aqueous sodium hydroxide or sodium carbonate.

Reductive Acetylation of Sclerotiorin (*with* N. B. Graham).—Zinc dust (6 g.) was added gradually to a solution of sclerotiorin (10 g.) and sodium acetate (5 g.) in boiling acetic anhydride (75 ml.) and after the vigorous reaction had subsided the mixture was heated under reflux for 15 min. The colourless solution was poured into water (250 ml.) and, on purification from alcohol, the precipitate gave a product in pale yellow needles (6 g.), m. p. 207—216°, which appeared to be a mixture [Found: C, 65·3, 65·2; H, 6·9, 6·5; Cl, 9·8%; *M* (Rast), 637, 647, 778; *M* (Menzies–Wright), 784, 908]. This product was insoluble in 2N-aqueous sodium hydroxide, had a negative ferric reaction in alcohol, and did not react with ammonia or alcoholic 2 : 4-dinitrophenylhydrazine sulphate. On repeated purification from alcohol this mixture (2 g.) ultimately furnished a fraction (0·4 g.), m. p. 220—222°, which appeared to be a substantially homogeneous substance (Found: C, 65·6; H, 6·1; Cl, 9·8%).

Interaction of Sclerotiorin with Ammonia and Primary Amines.—Sclerotiorin (4 g.) rapidly dissolved in aqueous ammonia (30 ml.; *d* 0·88) at room temperature, and 20 min. later the deep red solution was diluted with water (50 ml.), filtered, and poured into concentrated hydrochloric acid (35 ml.) and water (150 ml.) at 0°. Purification of the well-washed red precipitate from aqueous alcohol gave sclerotioramine in red needles (3·7 g.), m. p. 234° (decomp.) (Birkinshaw [5] gives m. p. 228—229°), $\lambda_{max.}$ 230, 345, and 504 mμ (log ε, 4·14, 4·60, and 3·83) (Found: C, 64·6, 64·7; H, 6·2, 6·0; N, 3·5, 3·5; Cl, 9·6. Calc. for $C_{21}H_{24}O_4NCl$: C, 64·6; H, 6·2; N, 3·6; Cl, 9·1%). Sclerotioramine, which readily forms a red solution in 2N-aqueous sodium carbonate or sodium hydroxide, is insoluble in 2N-aqueous sodium hydrogen carbonate, has a negative ferric reaction in alcohol, and forms an unstable yellow hydrochloride on treatment with hydrochloric acid.

[18] Badin and Pacsu, *J. Amer. Chem. Soc.*, 1945, **67**, 1353.

On addition of hydrazine hydrate (0·5 g.) to a solution of sclerotiorin (1 g.) in methanol (10 ml.), followed by dilution of the resulting red solution immediately with water (100 ml.), a red semicrystalline solid separated which on purification from aqueous methanol furnished *N-aminosclerotioramine* in purple needles (0·8 g.), m. p. 232° (decomp.) (Found: C, 62·6; H, 6·4; N, 6·4; Cl, 8·7. $C_{21}H_{25}O_4N_3Cl$ requires C, 62·4; H, 6·2; N, 6·9; Cl, 8·8%).

Addition of 33% aqueous methylamine (2 ml.) to a suspension of sclerotiorin (1 g.) in methanol (10 ml.) gave a purple red solution which on immediate dilution with water precipitated *N-methylsclerotioramine*, forming purple needles (0·9 g.), m. p. 212° (decomp.), from aqueous methanol (Found: C, 65·2; H, 6·4; N, 3·3; *N*-Me, 6·2; OMe, 0. $C_{22}H_{26}O_4NCl$ requires C, 65·5; H, 6·5; N, 3·5; *N*-Me, 7·2%).

A solution of sclerotiorin (1 g.) in alcohol (150 ml.), containing aniline (0·2 ml.), was kept at 50° for 1 hr. and diluted with water. Crystallised from dilute alcohol, the resultant precipitate gave the *aniline adduct* in yellow plates (1 g.), m. p. 169° (Found: C, 67·0, 67·0; H, 6·4, 6·1; N, 3·0, 2·7; Cl, 7·5. $C_{27}H_{30}O_5NCl$ requires C, 67·0; H, 6·2; N, 2·9; Cl, 7·3%). Addition of 2N-sulphuric acid (2 drops) or 2N-aqueous sodium hydroxide (2 drops) to a suspension of this adduct (1 g.) in alcohol (25 ml.) produced an immediate deep red solution, which was kept at room temperature for 0·5 hr. and diluted with water. Purified from aqueous methanol, the precipitate gave *N-phenylsclerotioramine* in red needles (0·9 g.), m. p. 189°, insoluble in aqueous or alcoholic sodium hydroxide solution (Found: C, 69·9; H, 6·0; N, 3·0; Cl, 7·6. $C_{27}H_{28}O_4NCl$ requires C, 69·6; H, 6·1; N, 3·0; Cl, 7·6%). The same derivative, m. p. and mixed m. p. 189°, was formed by interaction of sclerotiorin (1 g.) and aniline (0·5 g.) in alcohol (10 ml.) at room temperature for 48 hr.

Ozonolysis of Sclerotioramine.—A stream of ozone and oxygen was passed into a suspension of sclerotioramine (1 g.) in ethyl acetate (100 ml.) at room temperature for 25 min., the resulting red solution was evaporated in a vacuum, and the residual red glass treated with water (150 ml.). 12 Hr. later the intractable, red resin was removed and the solution distilled into aqueous 2 : 4-dinitrophenylhydrazine sulphate, giving 2 : 4-dimethylhex-2-enaldehyde 2 : 4-dinitrophenylhydrazone (0·1 g.), m. p. and mixed m. p. 159°.

Tetrahydrosclerotiorin.—A solution of sclerotiorin (5 g.) in acetic acid (100 ml.) containing a palladium catalyst (from 0·25 g. of palladium chloride and 1 g. of charcoal) was shaken in hydrogen until the absorption of gas was about 880 ml. (*ca.* 3 mol.); the orange solution gradually changed to pale yellow. Evaporation of the filtered solution in a vacuum left an oil which crystallised from methanol, giving tetrahydrosclerotiorin (mixed isomers) in pale yellow needles (3·25 g.), m. p. 141—144°, insoluble in cold 2N-aqueous sodium hydroxide, having $[\alpha]_D^{21}$ +215° (*c* 0·1 in EtOH) and $\lambda_{max.}$ 225, 343 mμ (log ε 4·13, 4·30 respectively) (Found: C, 64·2, 64·1, 64·1, 63·9; H, 7·0, 6·8, 6·9, 6·6; Cl, 9·9. Calc. for $C_{21}H_{27}O_5Cl$: C, 63·9; H, 6·9; Cl, 9·0%). Addition of 2N-aqueous sodium hydroxide to an alcoholic solution of this compound gave a deep orange solution which remained clear on dilution with water; on immediate acidification unchanged tetrahydrosclerotiorin was then precipitated.

By prolonged fractional crystallisation from alcohol, tetrahydrosclerotiorin, m. p. 143—144°, was resolved into β-*tetrahydrosclerotiorin*, m. p. 159°, $\lambda_{max.}$ 225, 343 mμ (log ε 4·15, 4·34), $[\alpha]_D^{21}$ +230° (*c* 0·11 in EtOH) (Found: C, 63·8; H, 6·6; Cl, 7·9%), together with α-*tetrahydrosclerotiorin*, m. p. 112°, $\lambda_{max.}$ 225, 343 mμ (log ε 4·15, 4·34), $[\alpha]_D^{21}$ +206° (*c* 0·15 in EtOH) (Found: C, 63·9; H, 7·0%). A mixture of α- and β-tetrahydrosclerotiorin had m. p. *ca.* 135°.

Concentration of the mother-liquors from the purification of crude tetrahydrosclerotiorin gave a yellow oil.

Hydrogenation of sclerotiorin (5 g.) in alcohol (100 ml.) gave tetrahydrosclerotiorin (3·1 g.) along with an oil.

Oxidation of Tetrahydrosclerotiorin.—A solution of chromic oxide (1·7 g.) in acetic acid (50 ml.) was added in 24 hr. to tetrahydrosclerotiorin (1 g.) in acetic acid (40 ml.) and, after removal of the solvent in a vacuum, the acidic fraction was isolated from an ethereal solution of the oxidation product with aqueous sodium hydrogen carbonate and purified by distillation at 115°/1 mm. Thus obtained, 4 : 6-dimethyl-*n*-octanoic acid was converted into the *p*-bromophenacyl ester which separated from aqueous methanol in plates, m. p. 31—34°, undepressed on admixture with the ester of the authentic acid prepared by the hydrogenation of 4 : 6-dimethylocta-2 : 4-dienoic acid; the infrared absorption spectra of the two specimens were identical.

Dihydrosclerotiorin (with N. B. Graham).—When sclerotiorin (5 g.) was added quickly to a

stirred mixture of acetic anhydride (15 ml.) and hydriodic acid (15 ml.; *d* 1·7) at 80°, iodine was liberated immediately. 5 Min. later the mixture was poured into an excess of concentrated aqueous sodium sulphite, and next day the solid was collected and purified from methanol, giving *dihydrosclerotiorin* in pale yellow needles (0·5—1·0 g.), m. p. 192° (decomp.), $[\alpha]_D^{21}$ +184°, with a negative ferric reaction (Found: C, 64·1, 64·1; H, 6·6, 6·7; Cl, 8·9, 8·9; I, 0. $C_{21}H_{25}O_5Cl$ requires C, 64·2; H, 6·4; Cl, 9·0%). The conditions for this reaction are critical, particularly the temperature which must be within the limits 65—80°. Dihydrosclerotiorin, which sublimes unchanged, is readily soluble in alcohol and insoluble in cold 2N-aqueous sodium hydroxide. Addition of 2N-aqueous sodium hydroxide to the compound dissolved in methanol gives an orange solution which remains clear on dilution with water; on immediate acidification unchanged dihydrosclerotiorin is precipitated.

Larger quantities of dihydrosclerotiorin were prepared by the following somewhat less tedious procedure. Sclerotiorin (25 g.) was added rapidly to a stirred mixture of hydriodic acid (50 ml.; *d* 1·7) and acetic acid (from 75 ml. of anhydride) at 75°, and 4 min. later the solution was poured into concentrated aqueous sodium hydrogen sulphite (500 ml.) at 0°. Collected immediately and purified from methanol, the solid gave dihydrosclerotiorin (2·5 g.), m. p. and mixed m. p. 192°. Repeated attempts under a variety of conditions failed to improve the yield of this product.

After treatment with hydrobromic acid under similar conditions sclerotiorin was recovered unchanged.

Ozonolysis of Dihydrosclerotiorin.—A stream of ozone and oxygen was passed through a solution of dihydrosclerotiorin (0·6 g.) in ethyl acetate (150 ml.) at room temperature for 40 min. and the solvent removed in a vacuum. Water (15 ml.) was added to the residual gum and next day the resulting solid was purified from alcohol, giving *dihydropentanorsclerotiorone* in yellow needles, m. p. 196—198°; mixed with dihydrosclerotiorin it had m. p. *ca.* 162° (Found: C, 56·6, 56·6, 56·4; H, 4·7, 4·7, 4·8; Cl, 11·1. $C_{16}H_{15}O_6Cl$ requires C, 56·8; H, 4·4; Cl, 10·5%). Distilled into 2 : 4-dinitrophenylhydrazine sulphate solution, the aqueous hydrolysate gave a precipitate of the 2 : 4-dinitrophenylhydrazone of (+)-α-methylbutyraldehyde in golden plates, m. p. and mixed m. p. 128—129°.

Exhaustive Hydrogenation of Sclerotiorin.—A solution of sclerotiorin (5 g.) in acetic acid (100 ml.) containing palladium–charcoal (from 1 g. of charcoal and 0·25 g. of palladium chloride) was shaken in hydrogen until absorption ceased (*ca.* 5 hr.); about 6 mol. (1700 ml.) were absorbed. Removal of the solvent left a colourless oil which crystallised from light petroleum (b. p. 60—80°), giving *sclerotinol* in needles (1·8 g.), m. p. 86°, with a negative ferric reaction, $[\alpha]_D^{20}$ +3·26° (*c* 2·36 in $CHCl_3$), $[M]_D^{20}$ +1108°, $\lambda_{max.}$ 299 mμ (log ε 3·34) (Found: C, 66·9, 67·0, 66·9; H, 8·3, 8·1, 8·4; Cl, 10·5, 10·5. $C_{19}H_{29}O_3Cl$ requires C, 66·9; H, 8·6; Cl, 10·4%). This compound, which is readily soluble in the usual organic solvents except light petroleum, readily dissolves unchanged in cold 2N-aqueous sodium hydroxide.

From the concentrated mother-liquors left from purification of sclerotinol, *sclerotol* was obtained which separated from light petroleum (b. p. 60—80°) in needles (0·3 g.), m. p. 147°, with a negative ferric reaction, $[\alpha]_D^{18}$ +5·2° (*c* 2·27 in $CHCl_3$), $[M]_D^{19}$ +1757°, $\lambda_{max.}$ 287 mμ (log ε 3·37) (Found: C, 67·2, 67·1; H, 8·1, 7·8; Cl, 10·5, 10·6. $C_{19}H_{27}O_3Cl$ requires C, 67·3; H, 8·0; Cl, 10·5%). The yield of sclerotol, which was always small, was very variable and occasionally nil.

When tetrahydrosclerotiorin (5 g.) in acetic acid (100 ml.) was hydrogenated under the same conditions until the absorption of hydrogen (1120 ml., 4 mol.) ceased, sclerotinol (2·5 g.) and sclerotol (0·35 g.) were obtained. Similarly, dihydrosclerotiorin (1 g.) in acetic acid (100 ml.) gave sclerotinol, m. p. and mixed m. p. 86° (256 ml., 4·2 mol. of hydrogen were absorbed).

Prolonged hydrogenation of sclerotiorin or tetrahydrosclerotiorin in alcohol or ethyl acetate resulted in the uptake of the requisite quantities of hydrogen, but the products were oils which did not yield crystalline material before or after chromatography from light petroleum on silica or neutralised aluminium oxide.

When a platinum catalyst was employed the hydrogenation of sclerotiorin (1 g.) or of tetrahydrosclerotiorin (1 g.) in alcohol (25 ml.) or acetic acid (25 ml.) proceeded comparatively rapidly (*ca.* 1 hr.), giving sclerotinol (25 mg.), m. p. 85—86°, as the only isolable product; this was separated with difficulty from the accompanying gum by chromatography from light petroleum (b. p. 60—80°) on silica gel, followed by crystallisation from light petroleum (b. p. 60—80°).

Derivatives of Sclerotinol.—By the standard method, sclerotinol gave (0·65 g.) the *di-p-nitrobenzoate*, needles (1·2 g.) (from alcohol), m. p. 152—153° (Found: C, 62·3, 61·9; H, 5·7, 5·5; N, 4·2, 4·1. $C_{33}H_{35}O_9N_2Cl$ requires C, 62·0; H, 5·5; N, 4·4%). The 2 : 4-*dinitrophenylhydrazone* of this di-*p*-nitrobenzoate crystallised from aqueous alcohol in yellow needles, m. p. 203° (Found: C, 57·1; H, 5·0; N, 9·9; Cl, 4·3. $C_{39}H_{39}O_{12}N_6Cl$ requires C, 57·2; H, 4·8; N, 10·3; Cl, 4·3%). Sclerotinol, by the sodium acetate or pyridine method, furnished the *diacetate* (in high yield), which separated from light petroleum (b. p. 60—80°) in needles, m. p. 98° (Found: C, 64·8; H, 7·9; Cl, 8·6. $C_{23}H_{33}O_5Cl$ requires C, 65·0; H, 7·8; Cl, 8·4%). Deacetylation of this diacetate (0·2 g.) in alcohol (10 ml.) with 10% aqueous potassium hydroxide (5 ml.) for 3 hr. regenerated sclerotinol (0·15 g.), m. p. and mixed m. p. 86°, after purification. The 2 : 4-*dinitrophenylhydrazone* of this acetate separated from aqueous alcohol in pale yellow needles, m. p. 123° (Found: C, 57·6; H, 6·2; N, 9·3; Cl, 5·9. $C_{29}H_{27}O_8N_4Cl$ requires C, 57·5; H, 6·0; N, 9·2; Cl, 5·7%).

By the methyl sulphate–potassium carbonate method for 2 hr. sclerotinol (0·5 g.) gave the *dimethyl ether* (0·4 g.), b. p. 120°/0·01 mm., $\lambda_{max.}$ 274 mμ (log ε 2·86) [Found: C, 68·6; H, 9·3; Cl, 9·6; OMe, 16·8. $C_{19}H_{27}OCl(OMe)_2$ requires C, 68·4; H, 9·0; Cl, 9·6; OMe, 16·8%]. Methyl sulphate and aqueous alkali afforded a poor yield of the same product. Demethylation of di-*O*-methylsclerotinol (0·4 g.) with a boiling mixture of hydriodic acid (8 ml.; *d* 1·7) and acetic acid (from 6 ml. of acetic anhydride) for 30 min. regenerated sclerotinol (0·1 g.), m. p. and mixed m. p. 86°. The *oxime* of di-*O*-methylsclerotinol was obtained as an oil which was purified by distillation at 140—145°/0·01 mm. and then slowly crystallised, having m. p. *ca.* 25° [Found: C 65·9; H, 8·8; Cl, 9·1; N, 4·0; OMe, 16·2. $C_{19}H_{28}ONCl(OMe)_2$ requires C, 65·7; H, 8·9; Cl, 9·2; N, 3·7; OMe, 16·3%].

Derivatives of Sclerotol.—Prepared from sclerotol (0·3 g.) by pyridine–acetic anhydride on the steam-bath for ½ hr., the *diacetate* separated from light petroleum (b. p. 60—80°) in needles (0·3 g.), m. p. 106° (Found: C, 65·5; H, 7·6; Cl, 8·4. $C_{23}H_{31}O_5Cl$ requires C, 65·3; H, 7·4; Cl, 8·4%). Mixed with the acetate of sclerotinol it had m. p. *ca.* 90°. By the methyl sulphate–potassium carbonate method, sclerotol (0·5 g.) gave the *dimethyl ether* (0·3 g.), b. p. 125—130°/0·01 mm. [Found: C, 68·6; H, 8·5; Cl, 9·7; OMe, 16·8. $C_{19}H_{25}OCl(OMe)_2$ requires C, 68·7; H, 8·5; Cl, 9·7; OMe, 16·9%]. The *di-p-nitrobenzoate* of sclerotol separated from aqueous alcohol in needles, m. p. 106° (Found: C, 62·2; H, 5·6; N, 4·3; Cl, 5·5. $C_{33}H_{33}O_9N_2Cl$ requires C, 62·2; H, 5·2; N, 4·4; Cl, 5·6%), and gave a 2 : 4-*dinitrophenylhydrazone*, yellow needles, m. p. 122° (from aqueous alcohol) (Found: C, 57·2; H, 4·8; N, 10·5; Cl, 4·4. $C_{39}H_{37}O_{12}N_6Cl$ requires C, 57·3; H, 4·6; N, 10·3; Cl, 4·3%).

Reduction of Sclerotinol and of Di-O-methylsclerotinol.—A solution of the phenol (0·5 g.) in ether (10 ml.) was added slowly to lithium aluminium hydride (2 g.) in ether (100 ml.), and the mixture then heated under reflux for 2 hr. On isolation in the usual manner the *product* separated from light petroleum (b. p. 60—80°) in needles, m. p. 79°, $\lambda_{max.}$ 287 mμ (log ε 3·27) (Found: C, 66·4; H, 9·0; Cl, 10·1; O, 14·2. $C_{19}H_{31}O_3Cl$ requires C, 66·5; H, 9·1; Cl, 10·3; O, 14·0%). A mixture of this alcohol and sclerotinol had m. p. *ca.* 70°. The infrared absorption spectrum showed the absence of carbonyl groups.

A solution of di-*O*-methylsclerotinol (0·6 g.) in ether (15 ml.) was added slowly to lithium aluminium hydride (3 g.) in ether (100 ml.), and the mixture heated under reflux for 2 hr. The resulting *alcohol* was an oil (0·5 g.), b. p. 120—130°/0·01 mm., the infrared spectrum of which exhibited hydroxyl but not carbonyl absorption; it had $\lambda_{max.}$ 279 mμ (log ε 2·90) [Found: C, 68·1; H, 9·8; Cl, 9·6; OMe, 16·5. $C_{19}H_{29}OCl(OMe)_2$ requires C, 68·0; H, 9·5; Cl, 9·6; OMe, 16·7%].

Dehydration of this alcohol (0·5 g.) with sodium hydrogen sulphate (2 g.) at 180° for 2 hr. gave the dehydration product (0·3 g.), b. p. 125°/0·01 mm., which did not show infrared hydroxyl absorption and had $\lambda_{max.}$ 279 mμ (log ε 3·01) [Found: C, 71·4; H, 9·4; Cl, 10·1; OMe, 17·8. $C_{19}H_{27}Cl(OMe)_2$ requires C, 71·4; H, 9·4; Cl, 10·1; OMe, 17·6%]. Ozonolysis of this compound in ethyl acetate or chloroform, followed by distillation of the product, gave an almost quantitative yield of di-*O*-methylsclerotinol, identified by the infrared absorption spectrum (Found: C, 68·7; H, 9·2%).

Beckmann Rearrangement of Di-O-methylsclerotinol Oxime.—A solution of the oxime (0·4 g.) in ether (15 ml.) was treated with thionyl chloride (1 drop), the solvent evaporated, water added, and the product isolated with ether and purified from light petroleum (b. p. 60—80°), giving a *product* in needles (0·35 g.), m. p. 125° [Found: C, 65·6; H, 8·9; N, 3·4; Cl, 9·2; OMe,

16·3. $C_{19}H_{28}ONCl(OMe)_2$ requires C, 65·7; H, 8·9; N, 3·7; Cl, 9·2; OMe, 16·3%]; the infrared absorption spectrum has a band at 1642 cm.$^{-1}$ (amide carbonyl [18]) which is not present in the spectrum of the oxime. This product was not hydrolysed by boiling 6N-alcoholic potassium hydroxide for 3 hr., boiling 35% sulphuric acid for 10 hr., or concentrated sulphuric acid at room temperature. It was unaffected by aqueous potassium permanganate solution in acetone at room temperature, by sodium in alcohol, or by lithium aluminium hydride in ether for 6 hr.

Action of Grignard Reagents upon Di-O-methylsclerotinol.—A solution of di-*O*-methylsclerotinol (0·6 g.) in ether (15 ml.) was added to an excess of phenylmagnesium bromide in ether (50 ml.), and the mixture was boiled for 1 hr., decomposed with ice and 2N-sulphuric acid, and extracted with ether. The residue left on evaporation of the extract was distilled at 140°/0·01 mm., giving the *phenyl derivative* (0·6 g.) which slowly crystallised in needles, m. p. *ca.* 20° [Found: C, 72·4; H, 8·8; Cl, 8·2; OMe, 13·7. $C_{25}H_{33}OCl(OMe)_2$ requires C, 72·6; H, 8·7; Cl, 8·0; OMe, 13·9%].

Similarly interaction of di-*O*-methylsclerotinol (0·3 g.) and excess of methylmagnesium iodide furnished the *methyl derivative* (0·2 g.), b. p. 130°/0·01 mm. [Found: C, 69·9; H, 9·2; Cl, 8·9; OMe, 15·6. $C_{26}H_{31}OCl(OMe)_2$ requires C, 68·6; H, 9·7; Cl, 9·2; OMe, 16·1%]. The absorption at 3670 cm.$^{-1}$ indicates the presence of a tertiary hydroxyl group.

The ultraviolet absorption spectra were determined with a Unicam S.P. 500 spectrophotometer in 95% alcohol, and the infrared spectra in Nujol with a Grubb-Parsons double-beam spectrophotometer. The analyses were by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, June 21st*, 1957.]

[18] Ref. 13, p. 176.

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987. *The Chemistry of Fungi. Part XXIX.*[1] *The Degradation of Di- and Tetra-hydrosclerotiorin with Alkali.*

By N. B. GRAHAM, H. PAGE, ALEXANDER ROBERTSON, R. B. TRAVERS, K. TURNER, and W. B. WHALLEY.

The degradation of tetrahydrosclerotiorin with alkali affords hydrochloric acid, formic acid, traces of 4 : 6-dimethyl-*n*-octanoic acid, and a dihydroxynaphtha-*p*-quinone (tetrahydrosclerotoquinone), $C_{19}H_{22}O_2(OH)_2$. The genesis, degradation, and structure of this quinone are discussed and possible formulæ deduced. Dihydrosclerotiorin undergoes an analogous series of transformations.

ON degradation with alkali sclerotiorin (I) gives formic, hydrochloric, and 4 : 6-dimethylocta-2 : 4-dienoic acid as the only characterisable fragments.[1] Under similar conditions tetrahydrosclerotiorin furnishes, in addition to formic, hydrochloric, and negligible amounts of the expected 4 : 6-dimethyl-*n*-octanoic acid, a product, named tetrahydrosclerotoquinone, $C_{19}H_{22}O_2(OH)_2$. This is shown to be a dihydroxynaphtha-*p*-quinone, forming a di-*O*-methyl ether, $C_{19}H_{22}O_2(OMe)_2$, and a di-*O*-acetate, $C_{19}H_{22}O_2(OAc)_2$, and on general grounds and in keeping with the molecular rotation is held to retain the saturated side-chain present in the parent compound. The remarks[1] regarding the existence of pairs of diastereoisomerides from the mixture of α- and β-tetrahydrosclerotiorin, m. p. 142—144°, apply to this quinone. In the present instance a second isomeride has not been detected. Reductive acetylation of tetrahydrosclerotoquinone gives tetra-*O*-acetyltetrahydrosclerotoquinol. Since the ultraviolet absorption of a chromophore is but little affected by substitution with acetoxyl groups,[2] a comparison of the ultraviolet

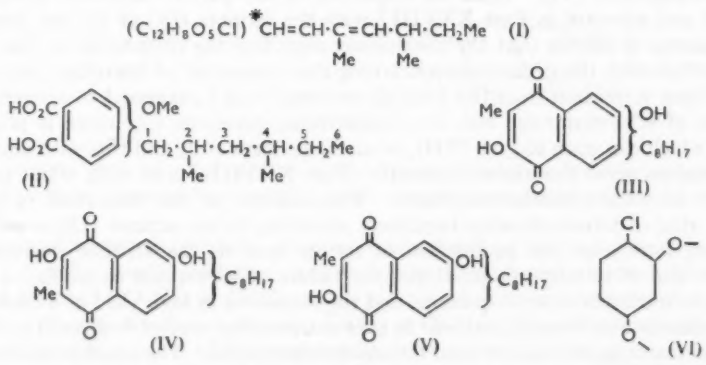
[1] Part XXVIII, Eade, Page, Robertson, Turner, and Whalley, preceding paper.
[2] Cooke, Macbeth, and Winzor, *J.*, 1939, 878.

absorption spectra of tetrahydro- and di-*O*-acetyltetrahydro-sclerotoquinone and tetra-*O*-acetyltetrahydrosclerotoquinol with those of 2-hydroxy-1 : 4-naphthaquinone, 1 : 4-naphthaquinone, and naphthalene respectively (cf. Table) indicates that tetrahydro-sclerotoquinone is a naphthalene derivative. In addition, the spectral data clearly show that sclerotoquinone is a 1 : 4- and not a 1 : 2-quinone,[2] in agreement with the failure of tetrahydrodi-*O*-methylsclerotoquinone to form a quinoxaline derivative.

As expected, the main absorption peaks in the spectra of the acetates derived from tetrahydrosclerotoquinone and tetrahydrosclerotoquinol are shifted to wavelengths 10—15 mμ longer than those for the corresponding naphthalene, owing to the bathochromic effect of the alkyl substituents (see Table).

Compound	$\lambda_{max.}$ (mμ)	log ε	Compound	$\lambda_{max.}$ (mμ)	log ε
Tetrahydrosclerotoquinone	273	4·56	2-Hydroxy-1 : 4-naphtha-quinone [2]	244	4·20
	307	4·19		276	4·20
	347	3·75		331	3·45
Di-*O*-acetyltetrahydrosclerotoquinone	258	4·48	1 : 4-Naphthaquinone [2]	246	4·28
	276	4·30		256	4·13
	342	3·58		334	3·44
Tetra-*O*-acetyltetrahydrosclerotoquinol	234	4·94	Naphthalene [2]	220	5·05
	289	3·79		275	3·75
	336	1·89		314	2·50

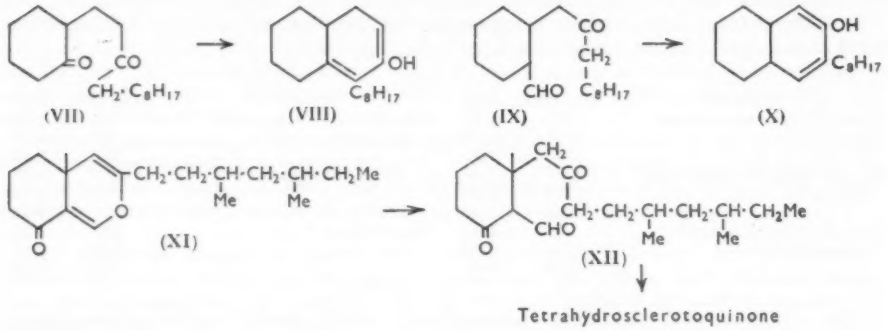
On oxidation with potassium permanganate tetrahydrodi-*O*-methylsclerotoquinone gave an optically active *x*-(2 : 4-dimethyl-*n*-hexyl)-*y*-methoxyphthalic acid (II) which forms an anhydride having infrared absorption at 1845 and 1721 cm.$^{-1}$ and readily yielding an anilic, a toluidic, and a β-naphthylamic acid. The composition of the methoxyphthalic acid and its derivatives shows that, in the oxidation of the *p*-quinonoid ring of tetrahydrodi-*O*-methylsclerotoquinone, a *C*-methyl and a methoxyl group have been removed and hence the quinone may be represented as (III). Since on demethylation the methoxyphthalic acid furnished a hydroxyphthalic acid which has a negative ferric reaction the hydroxyl group cannot be in the *o*-position to either of the carboxyl groups, and the formula for tetrahydrosclerotoquinone may be expanded to (IV) or (V). Further, from the composition of the methoxyphthalic acid and in agreement with its molecular rotation, the compound and hence sclerotoquinone and its dimethyl ether retain a C_8H_{17} residue from the saturated side-chain present in tetrahydrosclerotiorin.



From the failure of repeated attempts to prepare from sclerotiorin a quinone analogous to tetrahydrosclerotoquinone it appears reasonable to conclude that the presence of a

[2] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Ed. Arnold, London, 1954, p. 122.

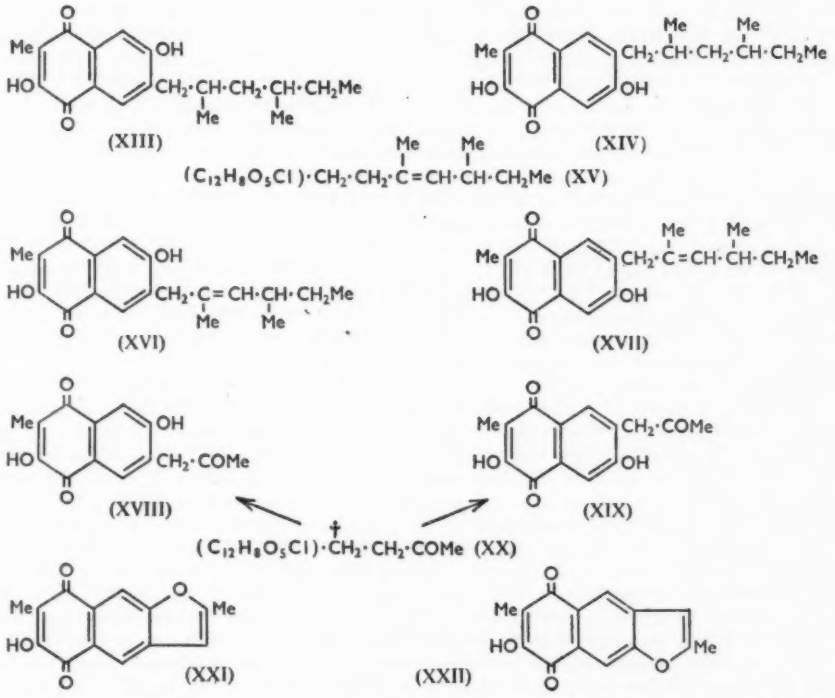
methylene group at the position marked * in the side-chain [see formula (I)] is essential for the formation of tetrahydrosclerotoquinone and that this compound is an artefact arising by a modification of the sclerotiorin kernel. Further, in the formation of the quinone the original side-chain C_9H_{19} of tetrahydrosclerotiorin has been shortened by a methylene group, which is involved in the formation of the benzene ring retaining the residual C_8H_{17} alkyl residue, exemplified in the cyclisation of (VII) to (VIII) or (IX) to (X).



From the methods of formation, the properties, and information available on the partial structure of sclerotinol [1] and of tetrahydrosclerotoquinone it seems reasonable to conclude that sclerotiorin contains a potentially aromatic ring system, aromatisation of which is invariably accompanied by simultaneous elimination of two carbon atoms or of a C_2 residue, leading to the benzene ring in sclerotinol and sclerotol [1] and to the quinonoid ring of tetrahydrosclerotoquinone. Further, the chlorine atom, which is attached to the aromatic ring of sclerotinol and sclerotol, is presumably contained in the parent hydroaromatic ring of sclerotiorin. Under the alkaline conditions obtaining during the transformation of tetrahydrosclerotiorin into tetrahydrosclerotoquinone the halogen atom is replaced by an oxygen system and it therefore seems likely that in the hydroaromatic unit of the sclerotiorin kernel the chlorine atom and the two oxygen atoms possess the relative arrangement (VI). From an inspection of the partial structures developed for sclerotinol and sclerotol in Part XXVIII [1] with the formula (IV) or (V) for tetrahydrosclerotoquinone it follows that the conclusions regarding the orientation of this quinone are compatible with the deductions concerning the orientation of sclerotinol and sclerotol and with their formation from the kind of structural unit [1] suggested to account for the production of sclerotioramine and its *N*-substituted products, *i.e.*, there is present the unit (XI) which can open to give (XII), or an enolic form of it, and this with ammonia or primary amines gives the amino-derivative (Part XXVIII) [1] and with alkali undergoes cyclisation to tetrahydrosclerotoquinone. This concept of the formation of the non-quinonoid ring of tetrahydrosclerotoquinone according to the scheme (IX) ⟶ (X) also rationalises, *inter alia*, the production of formic acid in the alkaline degradation of sclerotiorin and of tetrahydrosclerotiorin, the failure of sclerotiorin to produce a quinone analogous to tetrahydrosclerotoquinone, and the formation in high yield of **4 : 6**-dimethylocta-**2 : 4**-dienoic acid from sclerotiorin in contrast with the negligible quantity of **4 : 6**-dimethyl-*n*-octanoic acid obtained from tetrahydrosclerotiorin. The conclusions concerning tetrahydrosclerotoquinone and its degradation are also in agreement with the deduction, from the orientation of sclerotinol, that the C_{10} residue of sclerotiorin is separated from the aromatic ring of sclerotinol by one carbon atom present as a methylene group.[1] On these views it seems clear that the phenolic hydroxyl group retained as methoxyl in the phthalic acid residue, prepared from tetrahydrosclerotoquinone, is derived from the

oxygen which is present as the carbonyl group in the dienoic acid and consequently the structure of tetrahydrosclerotoquinone is reduced to one of the alternatives (XIII) or (XIV).

In confirmation of the hypothesis that a methylene group at position * of the side-chain (cf. I) in sclerotiorin derivatives is essential for the quinone formation, it has been found that degradation of dihydrosclerotiorin (XV) [1] by alkali leads to simultaneous elimination of two carbon atoms and formation of a dihydroxynaphtha-*p*-quinone (dihydrosclerotoquinone), $C_{19}H_{20}O_2(OH)_2$, which readily yields a di-*O*-methyl ether, a di-*O*-acetate, and, on reductive acetylation, tetra-*O*-acetyldihydrosclerotoquinol, $C_{19}H_{20}(OAc)_4$. Like tetrahydrosclerotoquinone, dihydrosclerotoquinone does not form a quinoxaline derivative,



and the ultraviolet absorption spectra of the quinone diacetate and quinol tetra-acetate indicate that the compound is a naphtha-*p*-quinone and hence may be formulated as (XVI) or (XVII).

Ozonolysis of tetra-*O*-acetyldihydrosclerotoquinol and subsequent deacetylation of the product followed by aerial oxidation gave an acetonyl-hydroxy-*p*-quinone, dihydropentanorsclerotoquinone (XVIII) or (XIX) whose partial orientation is confirmed by its conversion on sublimation into a coumarone, (XXI) or (XXII); this coumarone was originally isolated in the purification of the acetonyl-hydroxy-quinone. The quinone (XVIII) or (XIX) is also obtained by the alkaline degradation of the compound [1] (XX) in which the requisite methylene group involved in the naphthaquinone formation is present at the carbon atom marked † in formula (XX). The production of a coumarone derivative in this manner serves to substantiate the relative positions of the hydroxyl and acetonyl residue in the benzenoid ring of the naphthaquinone derived from dihydrosclerotiorin. From this

it follows that dihydrosclerotoquinone may be formulated as (XVI) or (XVII) and therefore tetrahydrosclerotoquinone is represented by (XIII) or (XIV).

With dihydrosclerotoquinone there was obtained from the compound (XX) a small amount of a chlorine-containing, non-quinonoid phenol, $C_{14}H_{13}O_4Cl$, the yield of which can be somewhat increased by lowering the temperature of alkaline degradation. Since it cannot be converted into dihydropentanorschlerotoquinone (XVIII or XIX) under the standard conditions this compound does not appear to be an intermediate in the quinone formation.

Experimental

Degradation of Tetrahydrosclerotiorin with Alkali.—(*a*) Tetrahydrosclerotiorin (2 g.), zinc dust (3 g.), and 5% aqueous potassium hydroxide (100 ml.) were heated under reflux in nitrogen for 5 min. and the effluent gases were passed into a solution of 2 : 4-dinitrophenylhydrazine sulphate to trap volatile carbonyl compounds; a precipitate was not formed. The cooled, filtered mixture was acidified and the precipitate and solution extracted with ether (4 × 20 ml). The combined extracts were washed successively with aqueous 2N-sodium hydrogen carbonate, 2N-sodium carbonate, and 2N-sodium hydroxide, and the washings were acidified. The sodium hydrogen carbonate extract did not give a precipitate and the caustic extract gave an intractable red gum. From the aqueous sodium carbonate washings there was obtained an orange-brown solid (1·4 g.) which was purified by sublimation at 200°/0·005 mm., followed by crystallisation from methanol, giving *tetrahydrosclerotoquinone* in orange plates (0·7 g.), with a port-wine ferric reaction in alcohol, $\lambda_{max.}$ 273, 310, 345 mμ (log ε 4·50, 4·24, 3·80 respectively), and m. p. 218° [Found: C, 72·1, 72·1, 72·1; H, 7·6, 7·7, 7·6; Cl, 0%; *M* (Rast), 329. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·7%; *M*, 316], $[\alpha]_D^{20}$ 6·6° (*c* 1·37 in EtOH), $[M]_D^{20}$ +2085°. This compound is readily soluble in the usual organic solvents except light petroleum (b. p. 60—80°), and in 2N-aqueous sodium hydroxide or 2N-aqueous sodium carbonate gives a purple solution. A rather smaller yield of the same product was obtained in the absence of zinc dust.

(*b*) To ensure the absence of traces of acetic acid retained from its purification tetrahydrosclerotiorin (10 g.), dissolved in ether (700 ml.), was washed successively with 2N-aqueous sodium hydrogen carbonate (6 × 50 ml.) and water (4 × 70 ml.), and recovered by drying and evaporation. Degradation of the compound in batches (2 g. each) was performed as described in (*a*). The combined alkaline solutions were filtered, acidified with sulphuric acid, again filtered, and distilled in a current of steam until the distillate was no longer acidic; the volume of solution being distilled was maintained by the addition of distilled water as required. The distillate contained chloride ions and was neutralised with 0·1N-sodium hydroxide and evaporated, leaving a residue of colourless sodium salts (1·5 g.). Interaction of this with *o*-phenylenediamine in the usual manner gave benziminazole (0·8 g.) in needles, m. p. and mixed m. p. 190° (mixed m. p. with 2-methylbenziminazole, *ca.* 132°). The picrate had m. p. and mixed m. p. 228° (admixed with 2-methylbenziminazole picrate, it had m. p. 180—186°).

The 2 : 4-*dinitrophenylhydrazone* of tetrahydrosclerotoquinone separated from aqueous alcohol in orange needles, m. p. 242° (decomp.) (Found: N, 11·7. $C_{25}H_{28}O_7N_4$ requires N, 11·3%). The *di*-O-*methyl ether* was prepared by the methyl sulphate–potassium carbonate method, purified by chromatography on aluminium oxide from benzene, and crystallised from methanol, forming yellow prisms (0·5 g.), m. p. 55° [Found: C, 73·2; H, 8·3; OMe, 18·5. $C_{19}H_{23}O_2(OMe)_2$ requires C, 73·2; H, 8·2; OMe, 18·0%]. This ether was readily soluble in the usual organic solvents, had a negative ferric reaction in alcohol, and gave a 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate in red prisms, m. p. 211° (decomp.) [Found: N, 10·7; OMe, 11·8. $C_{25}H_{26}O_5N_4(OMe)_2$ requires N, 10·7; OMe, 11·8%].

Tetrahydrosclerotoquinone (0·5 g.) with acetic anhydride (4 ml.) with a drop of sulphuric acid, sodium acetate (0·1 g.), or pyridine, on the steam-bath for ½ hr., gave the *diacetate*, which separated from methanol in yellow needles (0·4 g.), m. p. 94°, $[\alpha]_D^{22}$ +8·3° (*c* 2·19 in EtOH), $\lambda_{max.}$ 258, 274, 340 mμ (log ε 4·45, 4·20, 3·54 respectively) (Found: C, 68·9, 69·0; H, 7·0, 7·2. $C_{23}H_{28}O_8$ requires C, 69·0; H, 7·1%). Reductive acetylation of the quinone (0·5 g.) with acetic anhydride (8 ml.), zinc dust (0·5 g.), and sodium acetate (0·5 g.) on the steam-bath for 15 min. gave *tetra*-O-*acetyltetrahydrosclerotoquinol* which separated from methanol in needles (0·4 g.), m. p. 88°, $\lambda_{max.}$ 234, 289, 336 mμ (log ε 4·94, 3·79, 1·90 respectively) [Found: C, 66·6; H, 7·0; CH_3·CO, 35·1. $C_{19}H_{22}(OAc)_4$ requires C, 66·7; H, 7·0; CH_3·CO, 35·4%].

Oxidation of Tetrahydrodi-O-methylsclerotoquinone.—A solution of potassium permanganate (3 g.) in water (80 ml.) was added gradually in 2 hr. to the di-*O*-methyl ether (0·5 g.), in acetone (50 ml.), and 24 hr. later the mixture was clarified with sulphur dioxide, concentrated in a vacuum to 50 ml., and extracted with ether (3 × 25 ml.). The combined ethereal extracts were washed with 2N-aqueous sodium hydrogen carbonate (4 × 20 ml.), and the washings acidified. Extraction of this with ether gave a *phthalic acid* which separated from benzene–light petroleum (b. p. 60—80°) in needles (0·15 g.), m. p. 72° [Found: C, 62·4; H, 8·0; OMe, 9·7. $C_{16}H_{21}O_4(OMe),H_2O$ requires C, 62·6; H, 8·0; OMe, 9·5%]. This acid, which is readily soluble in the usual organic solvents except in light petroleum, gave an intense fluorescein reaction. Distilled at 110°/0·01 mm., the acid (1 g.) furnished the *anhydride* (0·8 g.), m. p. 44°, $[\alpha]_D^{20}$ +16·3° (*c* 1·36 in EtOH), $[M]_D^{20}$ +4727° (Found: C, 69·6; H, 7·9; OMe, 11·2%; *M*, 295. $C_{16}H_{19}O_3{\cdot}OMe$ requires C, 70·3; H, 7·6; OMe, 10·7%; *M*, 290). Interaction of the anhydride (0·12 g.) with aniline (0·2 g.) in benzene (4 ml.) on the steam-bath for 5 min. yielded the *anilic acid* which separated from light petroleum (b. p. 60—80°) in needles (0·15 g.), m. p. 157° (Found: C, 72·2; H, 7·7; OMe, 8·1; N, 3·7. $C_{22}H_{25}O_3N{\cdot}OMe$ requires C, 72·0; H, 7·6; OMe, 8·1; N, 3·7%). Similarly prepared, the m-*toluidic acid* crystallised from benzene–light petroleum (b. p. 60—80°) in needles (0·2 g.), m. p. 148° (Found: C, 72·1; H, 7·8; N, 3·4. $C_{24}H_{31}O_4N$ requires C, 72·5; H, 7·9; N, 3·5%). The β-*naphthylamic acid* formed needles, m. p. 173°, from benzene (Found: C, 74·6; H, 7·4; N, 3·4; OMe, 7·0. $C_{26}H_{25}O_3N{\cdot}OMe$ requires C, 74·8; H, 7·2; N, 3·2; OMe, 7·2%).

Boiling for ½ hr. with methanol (3 ml.), water (20 ml.), and sodium hydroxide (2 g.) converted the anhydride into the phthalic acid (0·3 g.), m. p. and mixed m. p. 72° after purification from benzene–light petroleum (b. p. 60—80°).

The phthalic acid (1 g.) in ether (30 ml.) with an excess of ethereal diazomethane furnished the *dimethyl ester* (0·75 g.), b. p. 120—125°/0·01 mm. [Found: C, 66·5; H, 7·5; OMe, 25·1. $C_{14}H_{19}(OMe)(CO_2Me)_2$ requires C, 67·8; H, 8·4; OMe, 27·6%]. Treatment of this ester (0·5 g.) in ether (30 ml.) with ammonia at 0° gave an oil, which did not crystallise but on alkaline hydrolysis gave the phthalic acid (0·3 g.), m. p. and mixed m. p. 72°, and ammonia.

A mixture of the phthalic acid (0·2 g.), hydriodic acid (3 ml.; *d* 1·7), and acetic acid (from 2 ml. of anhydride) was heated under reflux for ½ hr., cooled, diluted with water (30 ml.), and extracted with ether (3 × 25 ml.). Evaporation of the washed, dried ethereal extracts furnished a pale yellow oil, with a negative ferric reaction and devoid of methoxyl groups, which readily dissolved in 2N-aqueous sodium hydrogen carbonate and gave an intense fluorescein reaction.

Degradation of Dihydrosclerotiorin with Alkali.—A mixture of dihydrosclerotiorin (2 g.), zinc dust (2 g.), and 5% aqueous potassium hydroxide (100 ml.) was heated under reflux in nitrogen for 5 min. and the resulting solution filtered, cooled, and added to an excess of 5N-hydrochloric acid. The pale brown precipitate was isolated with ether (5 × 50 ml.), and the solution washed successively with aqueous 2N-sodium hydrogen carbonate, 2N-sodium carbonate, and 2N-sodium hydroxide. On acidification of these extracts only the deep violet sodium carbonate solution furnished a precipitate, which was most readily purified by sublimation in a vacuum at 195°/0·005 mm. followed by crystallisation from alcohol, giving *dihydrosclerotoquinone* in bright orange needles (0·5 g.), m. p. 219—220° (decomp.), $\lambda_{max.}$ 271, 304 mμ (log ε 5·02, 4·14 respectively) (Found: C, 72·5; H, 6·7. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%). This quinone gives a violet solution in 2N-aqueous sodium carbonate and a red ferric reaction in alcohol. Methylation of the quinone (0·8 g.) by methyl sulphate–potassium carbonate for 2½ hr. furnished the *di-O-methyl ether* which separated from methanol in long yellow needles (0·7 g.), m. p. 98°, which changed to stout yellow prisms, m. p. 98°, on prolonged contact with the solvent [Found: C, 73·8; H, 8·0; OMe, 17·8. $C_{19}H_{20}O_2(OMe)_2$ requires C, 73·7; H, 7·7; OMe, 18·1%]. The ether had a negative ferric reaction in alcohol. On acetylation by pyridine–acetic anhydride dihydrosclerotoquinone (0·2 g.) gave the *di-O-acetate* in yellow plates (0·15 g.), m. p. 116°, with a negative ferric reaction (Found: C, 69·2; H, 6·4. $C_{23}H_{26}O_6$ requires C, 69·3; H, 6·6%).

Reductive acetylation of dihydrosclerotoquinone (0·8 g.) with sodium acetate (1 g.) and zinc dust (1 g.) in boiling acetic anhydride (5 ml.) for ½ hr. gave *tetra-O-acetyldihydrosclerotoquinol* in needles or prisms (0·65 g.), m. p. 139° (from methanol), $\lambda_{max.}$ 234, 280, and 289 mμ (log ε 4·91, 3·70, and 3·71 respectively) (Found: C, 67·1; H, 7·0. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7%). A stream of ozone and oxygen was passed into a solution of this tetra-acetate (0·5 g.) in ethyl acetate (50 ml.) at room temperature for 20 min., the solvent was removed *in vacuo*, and the

XUM

colourless residue treated with water (50 ml.). Next day a solution of the amorphous solid (0·2 g.) in methanol (10 ml.) was mixed with 2N-aqueous potassium hydroxide (5 ml.) and 5 min. later the violet solution was poured into 2N-hydrochloric acid (50 ml.), the precipitate was extracted with ether, and the extract was washed with 2N-aqueous sodium hydrogen carbonate. Obtained by the acidification of this violet alkaline solution, the solid was purified by sublimation at 210°/0·01 mm. to yield a mixture of pale yellow and orange products which were separated by fractional crystallisation from methanol, giving (*a*) a *furanonaphtha*-p-*quinone* in orange needles (20 mg.), m. p. 234°, sparingly soluble in methanol and insoluble in 2N-aqueous sodium hydrogen carbonate (Found: C, 69·3, 68·9; H, 4·5, 4·7. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%), and (*b*) an *acetonylhydroxynaphtha*-p-*quinone* in yellow needles (15 mg.), m. p. 225°, readily soluble in methanol and in 2N-aqueous sodium hydrogen carbonate to an intense violet solution (Found: C, 64·7, 64·5; H, 4·3, 4·0. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%). The furanonaphthaquinone was unchanged by sublimation at 220°/0·01 mm. but the acetonylhydroxynaphthaquinone gave a mixture of unchanged compound and the furanonaphthaquinone. The mixed m. p. of the two quinones was *ca.* 207°.

Degradation of Pentanordihydrosclerotiorone (XX) *with Alkali.*—(*a*) A mixture of this compound [1] (1 g.), zinc dust (1 g.), and 5% aqueous potassium hydroxide (100 ml.) was heated under reflux in nitrogen for 5 min., cooled, mixed with an excess of 2N-hydrochloric acid, and extracted with ether. The ethereal solution was washed with 2N-aqueous sodium hydrogen carbonate and the violet extract acidified, giving a solid which on sublimation in a vacuum furnished two products; (i) at 180°/0·01 mm., a colourless solid which on purification from methanol furnished a *phenol* (150 mg.) in needles, m. p. 224°, with an intense red-brown ferric reaction in alcohol and readily soluble in 2N-aqueous sodium hydrogen carbonate [Found: C, 60·2, 59·8; H, 4·9, 4·8; Cl, 13·5, 13·2, 13·0%; *M* (Menzies–Wright in C_6H_6), 279. $C_{14}H_{13}O_4Cl$ requires C, 60·0; H, 4·6; Cl, 12·7%; *M*, 280·5]; and (ii) at 210°/0·01 mm., a mixture of the two naphtha-*p*-quinones which was resolved as described previously into the furanonaphtha-*p*-quinone (10 mg.), m. p. and mixed m. p. 234°, and identical infrared spectra, and the acetonylhydroxynaphthaquinone (5 mg.), m. p. and mixed m. p. 225°, and identical infrared spectra.

(*b*) Compound (XX) (1 g.) was added to a mixture of 5% aqueous potassium hydroxide (50 ml.) and zinc dust (1 g.) at −3°, in nitrogen, and 15 min. later the filtered solution was added to an excess of 2N-hydrochloric acid. From an ethereal solution of the precipitate 2N-aqueous sodium hydrogen carbonate extracted a pale brown solid which was purified by repeated crystallisation from methanol, giving the phenol, m. p. and mixed m. p. 224°; this was more conveniently purified by sublimation at 180°/0·01 mm. followed by crystallisation from alcohol; the yield was 0·2 g. Under these conditions quinonoid substances were not formed. Heated under reflux with zinc dust (0·5 g.) and 5% aqueous potassium hydroxide (50 ml.) for 10 min., this phenol (0·2 g.) was recovered unchanged on acidification of the cooled solution (yield of compound, 0·1 g., m. p. and mixed m. p. 224°). The phenol furnishes iodoform under standard conditions.

The ultraviolet absorption spectra were determined in 95% alcohol with a Unicam S.P. 500 Spectrophotometer and the infrared spectral data were obtained in Nujol on a Grubb-Parsons double-beam spectrophotometer. The analyses were by Mr. A. S. Inglis, M.Sc. and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, July 1st*, 1957.]

988. *The Chemistry of Fungi. Part XXX.** apo*Sclerotioramine and its Derivatives.*

By H. C. Fielding, N. B. Graham, Alexander Robertson, R. B. Travers, and W. B. Whalley.

Sclerotioramine, $C_{21}H_{24}O_4NCl$, which yields an *O*-acetate, $C_{21}H_{23}O_3NCl{\cdot}OAc$, and an *N*-methyl ether, $C_{21}H_{23}O_4Cl{>}NMe$, exhibits the properties of a pyridone, and on reduction by various methods gives, with the simultaneous elimination of two carbon atoms, an aromatic, amphoteric derivative, *apo*sclerotioramine, $C_{19}H_{22}O_3NCl$, forming a di-*O*-acetate, $C_{19}H_{20}NCl(OAc)_2$; dihydrosclerotioramine furnishes the analogous dihydro*apo*sclerotioramine, $C_{19}H_{24}O_3NCl$. From their properties it appears that these products are complex derivatives of *iso*quinolone, and in agreement with this the ozonolysis of di-*O*-acetyl*apo*sclerotioramine yields a monobasic *iso*quinolonecarboxylic acid, *apo*sclerotaminic acid, $C_{11}H_6O_3NCl(OAc)_2$. As a result of extensive investigation of these compounds, in conjunction with a comparative examination of the analogous products from *N*-methylsclerotioramine, tentative structural formulæ for *apo*sclerotaminic acid and *apo*sclerotioramine and their derivatives are proposed.

The weakly basic amine, sclerotioramine,[1] the salts of which readily give yellow solutions in concentrated acids, regenerating the base on dilution with water, is readily soluble in 2N-aqueous sodium hydroxide from which it is recovered unchanged on immediate acidification, thus indicating that the compound contains an enolic or phenolic hydroxyl group. In agreement with the view [1] that the nitrogen atom is present in a heterocyclic ring, the base, which does not react with 2 : 4-dinitrophenylhydrazine, is decomposed by boiling acid or alkali with the production of acetic acid but without liberation of ammonia, and on methylation gives *N*-methylsclerotioramine identical with the product formed by the interaction of sclerotiorin with methylamine.[1] This methyl derivative, which is insoluble in aqueous sodium hydroxide, cannot be acetylated and does not absorb in the 3μ region. On acetylation sclerotioramine gives *O*-acetylsclerotioramine, $C_{21}H_{23}O_3NCl{\cdot}OAc$, which is insoluble in dilute alkalis but readily forms a yellow solution in dilute hydrochloric acid; deacetylation of the acetate with ammonia, or with dilute aqueous sodium hydroxide or carbonate, regenerates the parent base. That this acetyl derivative is an *O*-acetate is demonstrated by, *inter alia*, the fact that (*a*) the melting point of the acetate is about 100° below that of the parent base, compatible with the generalisation that, whilst *N*-acetylation gives a product with a melting point higher than that of the parent base, *O*-acetylation has the converse effect, (*b*) acetylsclerotioramine is a stronger base than sclerotioramine, whereas *N*-acetylation would reduce the basicity, and (*c*) the acetate exhibits a new infrared absorption band at 1779 cm.$^{-1}$ which is indicative of a vinylogous acetate. The formation of alkali-insoluble products by *O*-acetylation or *N*-methylation of sclerotioramine is compatible with the postulate that the nitrogen atom is contained in a heterocyclic system, and probably one of the pyridone or potential pyridone type.

Reduction of sclerotioramine with zinc and acetic acid or sodium hydroxide is accompanied by extrusion of two carbon atoms as acetic acid (approximately one mol.) and the formation of an amphoteric substance dideoxydinorsclerotioramine, $C_{19}H_{22}O_3NCl$, which we name *apo*sclerotioramine; this compound, which is much more readily isolated as the sulphate, $(C_{19}H_{22}O_3NCl)_2H_2SO_4$, forms a diacetate, $C_{19}H_{20}NCl(OAc)_2$. That this derivative is a di-*O*-acetate and does not contain an *N*-acetyl residue is indicated by the fact that (*a*) its melting point is lower than that of *apo*sclerotioramine, (*b*) the infrared absorption at 1770 cm.$^{-1}$, which is assigned to aromatic or vinylogous acetyl vibrations,

* Part XXIX, preceding paper.

[1] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4913.

is sufficiently strong to be attributed to the presence of two *O*-acetyl residues, and (*c*) the diacetate gives a hydrochloride, $C_{19}H_{20}NCl(OAc)_2$,HCl, showing that, compared with the parent compound, the basicity of the nitrogen has not been diminished; analysis of the hydrochloride shows that it contains an ionic and a non-ionic chlorine atom. From the general properties of di-*O*-acetyl*apo*sclerotioramine it appears that the parent base contains an aromatic nitrogen system with an aliphatic side chain and, further, the bathochromic shift of the ultraviolet absorption spectrum of the hydrochloride by 20—50 mμ for the various peaks (Fig. 1) indicates a quinoline or *iso*quinoline, and not a naphthylamine, nucleus.[2] Moreover, since the ultraviolet absorption spectrum of *apo*sclerotioramine does not show an appreciable shift in acidic or alkaline solution, the nucleus is probably in a quinolone or *iso*quinolone form.[2] in agreement with the pyridone character ascribed to the parent sclerotioramine.

Now, dihydrosclerotioramine, $C_{21}H_{26}O_4NCl$, which is formed by the action of ammonia on dihydrosclerotiorin,[1] is strictly analogous to sclerotioramine and on reduction with

FIG. 1. *Absorption spectra of* (*A*) *di*-O-*acetyl*-apo*sclerotioramine* [λ_{max} 225, 278, 320, 335 mμ ($\log_{10}$ ε 4·28, 4·36, 4·64, 4·62)], *and* (*B*) *di*-O-*acetyl*apo*sclerotioramine hydrochloride in* 0·1N-*hydrochloric acid* [$\lambda_{max.}$ 220, 291, 359, 405 mμ ($\log_{10}$ ε 4·34, 4·66, 3·98, 3·76)].

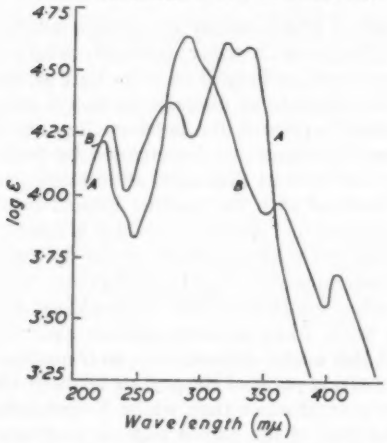
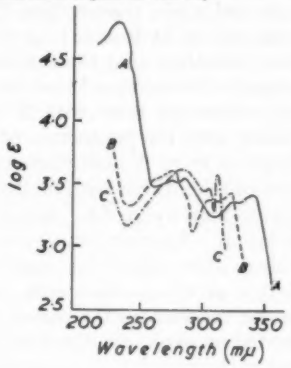


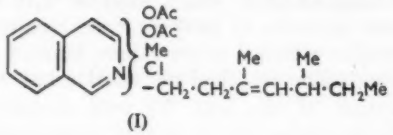
FIG. 2. *Absorption spectra of* (*A*) *di*-O-*acetyldihydro*apo*sclerotioramine* [$\lambda_{max.}$ 231, 275, 284, 339 mμ ($\log_{10}$ ε 4·75, 3·52, 3·54, 3·48), (*B*) iso*quinoline, and* (*C*) *quinoline. In* 0·5N-*hydrochloric acid the major peak at* 231 mμ *for di*-O-*acetyldihydro*apo*sclerotioramine was shifted to* 245 mμ.



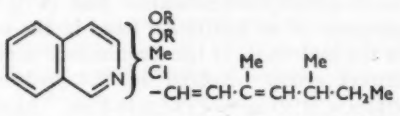
zinc dust and alkali furnishes dihydro*apo*sclerotioramine which is characterised as the diacetate, $C_{19}H_{22}NCl(OAc)_2$. For reasons advanced in the case of di-*O*-acetyl*apo*sclerotioramine, this derivative is a di-*O*-acetate and not *NO*-diacetyldihydro*apo*sclerotioramine. Since acetoxyl groups do not influence the ultraviolet absorption of aromatic systems [3] and the conjugated side-chain is now insulated from the aromatic chromophore the ultraviolet absorption of di-*O*-acetyldihydro*apo*sclerotioramine provides reasonably clear evidence regarding the *iso*quinoline nature of the nucleus present. Thus Fig. 2 shows that the absorption of this diacetate in neutral solution mimics that of *iso*quinoline (but not that of quinoline [4]) in intensity and in the relative position of the peaks but, as expected, at wavelengths longer by about 20 mμ. Consequently, on the pyridone hypothesis, di-*O*-acetyldihydro- and di-*O*-acetyl-*apo*sclerotioramine are in all probability *iso*quinolones, (I; R = Ac) and (II; R = Ac) respectively, containing in addition a nuclear *C*-methyl group. Collateral evidence for these views is provided below.

[2] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[3] Cooke, Macbeth, and Winzor, *J.*, 1939, 878.
[4] Cf. Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Ed. Arnold, London, 1954, p. 135.

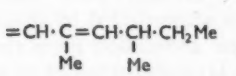
In agreement with earlier suggestions,[1] these partial formulæ imply that the alkyl side-chain of sclerotiorin is not involved in the formation of sclerotioramine and its analogues. This is substantiated by the formation of tetrahydrosclerotioramine, $C_{21}H_{28}O_4NCl$, from tetrahydrosclerotiorin and ammonia; this product is identical with the hydrogenation product of sclerotioramine and is converted, with the loss of two carbon atoms as acetic acid, by zinc and alkali into tetrahydro*apo*sclerotioramine analogous to *apo*sclerotioramine. Further, the ozonolysis of di-*O*-acetyl*apo*sclerotioramine involves the loss of eight carbon atoms corresponding to the residue (III) [five of which are accounted for by the isolation of (+)-α-methylbutyraldehyde[1]] with the formation of a monocarboxylic acid, $C_{11}H_6O_2NCl(OAc)_2$, which we name di-*O*-acetyl*apo*sclerotioraminic acid. This acid,



(I)

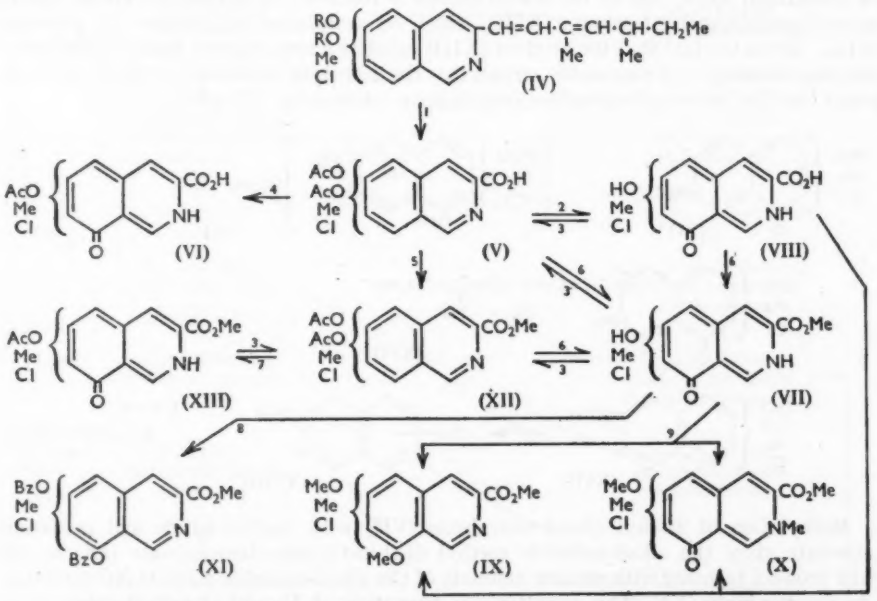


(II)



(III)

which must retain the *iso*quinolone nucleus of the precursor, forms a methyl ester and gives an intense red colour in alcohol with ferrous sulphate, indicating that the carboxyl group is conjugated with the aromatic residue and is in the *o*-position to the nitrogen atom,[5]



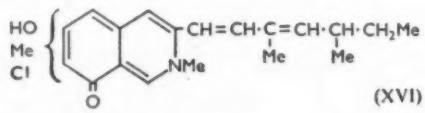
Reagents: 1, O_3. 2, NaOH. 3, Ac_2O–C_5H_5N. 4, NH_3. 5, CH_2N_2. 6, HCl–MeOH. 7, Chromatography. 8, BzCl–C_5H_5N. 9, MeI.

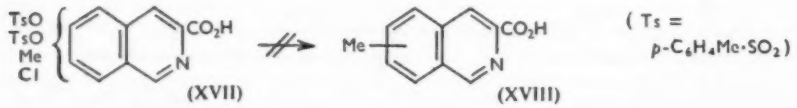
in agreement with previous hypotheses[1] concerning the nature of the progenitor of the nitrogen-containing ring in sclerotioramine. Consequently the partial formula (II; R = H) for *apo*sclerotioramine may be expanded to (IV; R = H), and di-*O*-acetyl*apo*-sclerotaminic acid and its methyl ester may be partially formulated as (V) and (XII)

[5] Ley, Schwarte, and Münnich, *Ber.*, 1924, **57**, 349.

respectively. The infrared absorption spectra of di-*O*-acetyl*apo*sclerotaminic acid and its ester confirm their relationship: the acid (V) has a broad band at about 2500 cm.$^{-1}$ with separate peaks at 2558 and 2457 cm.$^{-1}$, without exhibiting absorption in the 3000 cm.$^{-1}$ region as would be expected if the acidity of di-*O*-acetyl*apo*sclerotaminic acid (V) was due to the presence of phenolic or enolic hydroxyl groups; the ester (XII) absorbs at 1783 (vs) (aromatic acetyl) and 1721 cm.$^{-1}$ (vs) (conjugated ester),[6] thereby confirming that the carboxyl group of (V) is attached directly to an aromatic nucleus. It follows that the conjugated-diene side-chain is also conjugated with the nucleus of *apo*sclerotioramine as in (IV) and hence probably with the nucleus of sclerotioramine.

On treatment with aqueous ammonia di-*O*-acetyl*apo*sclerotaminic acid (V) gives mono-*O*-acetyl*apo*sclerotaminic acid (VI), the composition of which together with the appearance of an additional band in the infrared spectrum at 1650 cm.$^{-1}$ are consistent with the hydrolysis of the *iso*quinolone acetyl residue attached to the oxygen atom of the hydroxyl group involved in the hydroxy*iso*quinoline–*iso*quinolone relationship (A), ·C(OH):Ċ·CH:N· ⇌ ·CO·Ċ:CH·NH·. Esterification of the acid (V) with methanol–hydrogen chloride is accompanied by deacetylation, giving rise to methyl *apo*sclerotaminate (VII) which on acetylation gives rise to the methyl di-*O*-acetyl*apo*sclerotaminate (XII). The ester (VII) is also obtained by deacetylation of the di-*O*-acetyl*apo*sclerotaminic acid (V) to *apo*sclerotaminic acid (VIII) followed by esterification with methanolic hydrogen chloride. When methyl di-*O*-acetyl*apo*sclerotaminate (XII) is allowed to remain in contact with aqueous solvents for several weeks or is chromatographed from methanol on aluminium oxide, one of the acetyl groups is removed by hydrolysis, giving methyl mono-*O*-acetyl*apo*sclerotaminate (XIII), which on acetylation regenerates the precursor (XII). From the fact that the product (XIII) exhibits a new infrared band at 1650 cm.$^{-1}$ (vinylogous amide) it is reasonably certain that the deacetylation involves only the acetoxy-group [7] of the hydroxy*iso*quinoline–*iso*quinolone relationship (A) above.





Methylation of methyl *apo*sclerotaminate (VII) with methyl iodide and potassium carbonate gives the alkali-insoluble methyl di-*O*-methyl*apo*sclerotaminate (IX) as the chief product together with smaller amounts of the alkali-insoluble method *NO*-dimethyl-*apo*sclerotaminate (X). This simultaneous formation of *N*- and *O*-methyl ethers is an established characteristic of quinolones and *iso*quinolones.[8] Similarly, methylation of *apo*sclerotioramine sulphate with methyl iodide and potassium carbonate forms *NO*-dimethyl*apo*sclerotioramine (XIV), whilst methyl sulphate and potassium carbonate furnish *NOO*-trimethyl*apo*sclerotioramine methosulphate (XV). These products are

[6] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1956, p. 153.
[7] Gibson, Kynaston, and Lindsey, *J.*, 1955, 4340.
[8] Bogert and Seil, *J. Amer. Chem. Soc.*, 1907, **29**, 517.

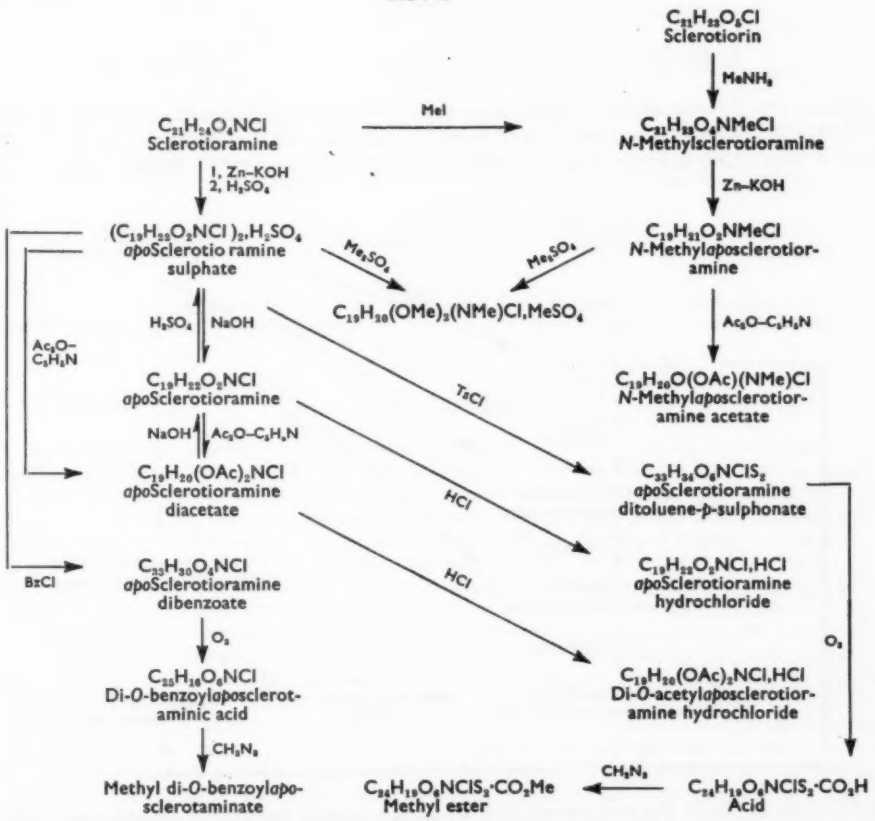
identical with the compounds obtained under similar conditions from *N*-methyl*apo*-sclerotioramine (XVI) (see below).

Benzoylation of *apo*sclerotioramine sulphate furnished the di-*O*-benzoate (IV; R = Bz), and on ozonolysis this product gave di-*O*-benzoyl*apo*sclerotaminic acid, which forms the methyl ester (XI), identical with the benzoylation product from methyl *apo*sclerotaminate (VII); this ester (XI) contains a *C*-methyl group, providing collateral evidence for the presence of this group in *apo*sclerotaminic acid and its derivatives. In agreement, a Kuhn–Roth estimation indicates the presence of three *C*-methyl residues in di-*O*-acetyl-*apo*sclerotaminic acid (V), *i.e.*, two from the acetyl groups and one in the nucleus.

Attempts to remove the halogen from *apo*sclerotaminic acid and its derivatives by a variety of methods failed: most of the starting material was always recovered.

*apo*Sclerotioramine (IV; R = H) gives a di-*O*-toluene-*p*-sulphonate (IV; R = *p*-$C_6H_4Me{\cdot}SO_2$) which is converted by ozonolysis into the di-*O*-toluene-*p*-sulphonate (XVII) of *apo*sclerotaminic acid, together with (+)-α-methylbutyraldehyde. Attempts to remove the halogen and toluene-*p*-sulphonyl residues by hydrogenation with Raney nickel,[9] (XVII) ⟶ (XVIII), were all unsuccessful. These reactions are summarised in Chart 1.

Chart 1.

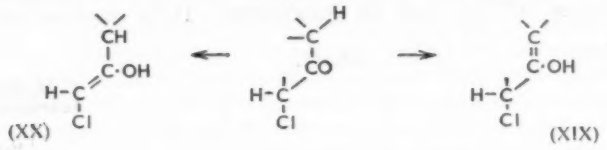


In experiments to determine whether *N*-methylsclerotioramine contains a lactone system, this compound, which is devoid of hydroxyl groups and is insoluble in aqueous

[9] Kenner and Murray, *J.*, 1950, 406; Cavillito and Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1927.

alkali, was dissolved in alcohol and treated with 2N-aqueous sodium hydroxide, giving a red solution. Dilution of this with water gave a somewhat unstable isomeride of the starting material, named *N*-methyl*iso*sclerotioramine, which exhibits strong absorption in the 3 μ region but has lost the carbonyl absorption at 1733 cm.$^{-1}$. Thus *N*-methyl*iso*-sclerotioramine is probably an enolic form of *N*-methylsclerotioramine, a view which is supported by formation of *NO*-dimethylsclerotioramine on methylation of sclerotioramine or of *N*-methylsclerotioramine with methyl sulphate and alkali. The infrared absorption at 1733—1745 cm.$^{-1}$ of, ***inter alia***, sclerotiorin, dihydro- and tetrahydro-sclerotiorin, sclerotioramine, di- and tetra-hydrosclerotioramine, and *N*-methylsclerotioramine may be allocated provisionally to an α-chloro-ketone system,[10] and consequently the disappearance of this peak in *N*-methyl*iso*- and in *NO*-dimethyl-sclerotioramine may be attributed to enolisation of the type (XIX) or (XX).

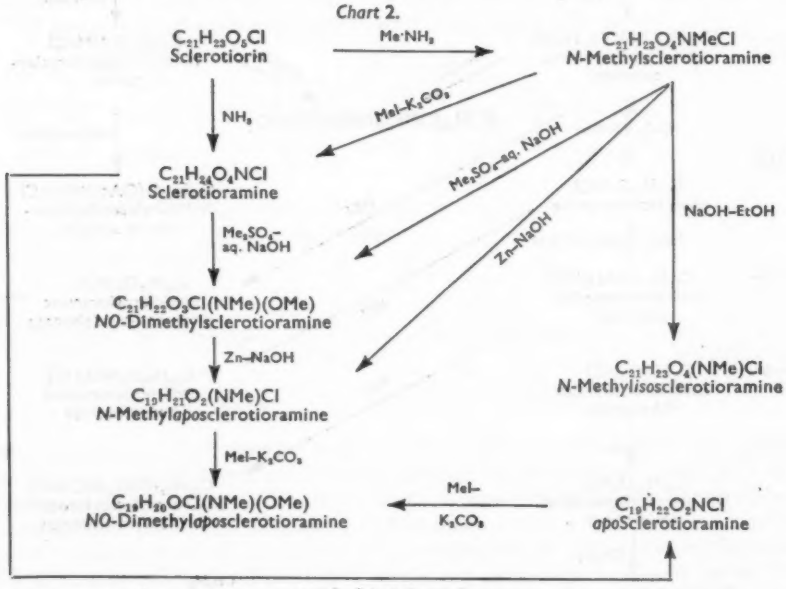
Except in the *apo*-series all derivatives of sclerotiorin exhibit infrared absorption at 771—775 cm.$^{-1}$, which has been previously [1] assigned tentatively to the C–Cl stretching



(XX) (XIX)

frequency.[11] This absorption persists in *N*-methyl*iso*- and in *NO*-dimethyl-sclerotioramine (at 773 and 774 cm.$^{-1}$ respectively) and hence, if allocation of the absorption at 771—775 cm.$^{-1}$ is correct, it is likely that the enolisation proceeds by way of (XIX) rather than

Chart 2.



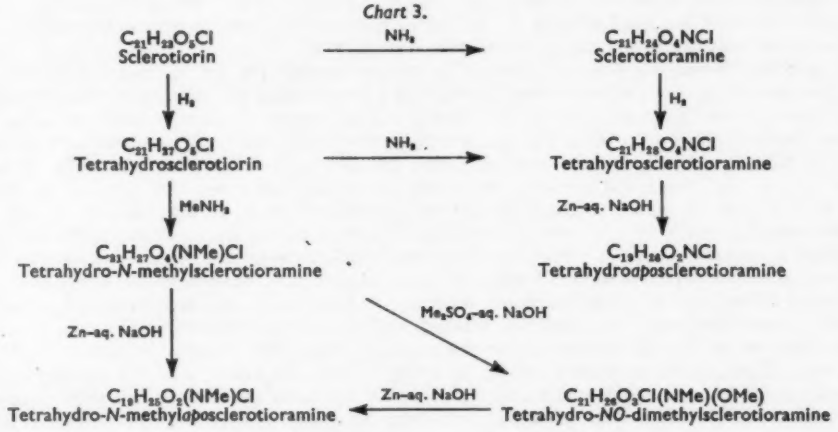
(XX), since in (XX) the C–Cl stretching frequency should undergo a considerable shift due to conjugation. Non-participation of the side-chain in this enolisation is shown by

[10] Ref. 6, p. 114.
[11] Ref. 6, p. 271.

(*a*) the formation of the analogous di- and tetra-hydro-*NO*-dimethylsclerotioramines from di- and tetra-hydrosclerotioramine respectively, (*b*) the production of 2 : 4-dimethylhexa-2-enaldehyde when *NO*-dimethylsclerotioramine is degraded with alkali, and (*c*) the reduction of both *N*-methyl- and *NO*-dimethyl-sclerotioramine with zinc–sodium hydroxide to give *N*-methyl*apo*sclerotioramine which is characterised as the monoacetate, $C_{22}H_{26}O_3NCl$. The formation of *NO*-dimethyl*apo*sclerotioramine (XIV) and of *NOO*-trimethyl*apo*sclerotioramine methosulphate (XV) from *apo*sclerotioramine and from *N*-methyl*apo*sclerotioramine provides additional evidence in support of the *iso*quinolone structures. These relations are summarised in charts 2 and 3.

On reduction with zinc and alkali tetrahydro-*N*-phenylsclerotioramine, which may be obtained from tetrahydrosclerotiorin [1] and aniline or by hydrogenation of *N*-phenylsclerotioramine, gave *N*-phenyl*apo*sclerotioramine.

Chart 3.



Experimental

O-Acetylsclerotioramine.—On being kept overnight a mixture of sclerotioramine (2 g.), acetic anhydride (20 ml.), and pyridine (0·5 g.) formed a deep red solution. After the removal of the excess of anhydride in a vacuum, the residue was dissolved in methanol (5 ml.) and slowly added to water (150 ml.), vigorously agitated. The precipitate was collected *immediately*, washed with water (150 ml.), and purified from methanol, giving *O-acetylsclerotioramine* in bright red needles (1·5 g.), m. p. 130° (Found: C, 63·6, 64·4; H, 6·3, 6·4; N, 3·4, 3·3. $C_{21}H_{23}O_3NCl{\cdot}OAc$ requires C, 64·0; H, 6·0; N, 3·2%). Very dilute acids, aqueous ammonia, or alkalis rapidly hydrolyse this acetate to sclerotioramine, m. p. and mixed m. p. 235° (decomp.).

N-Methylsclerotioramine.—Prepared from sclerotiorin and methylamine, this compound [1] was found to be dimorphous. Purification from aqueous solvents (*e.g.*, aqueous methanol) gave the base in purple needles, m. p. 225° (decomp.), whilst non-aqueous solvents (*e.g.*, alcohol) afforded red needles, m. p. 225° (decomp.) (Found: C, 65·8; H, 6·7. Calc. for $C_{22}H_{26}O_4NCl$: C, 65·4; H, 6·5%). A mixture of the two modifications had m. p. 225° and had identical infrared absorption spectra; the m. p. of the compound depended to some extent on the rate of heating.

Sclerotioramine [1] (1 g.) was methylated in boiling acetone (25 ml.) with potassium carbonate (5 g.) and methyl iodide (4 ml.) for 2 hrs. Repeated crystallisation of the product from aqueous methanol gave *N*-methylsclerotioramine in purple needles (0·9 g.), m. p. and mixed m. p. 218° (decomp.) (Found: C, 65·2; H, 6·2; N, 3·4; OMe, 0. Calc. for $C_{22}H_{26}O_4NCl$: C, 65·4; H, 6·5; N, 3·4%). Methylation of sclerotioramine (0·5 g.) by methyl sulphate–potassium carbonate for 45 min. gave *N*-methylsclerotioramine in purple needles (0·3 g.), m. p. and mixed

m. p. 218° (decomp.) after repeated crystallisation from aqueous methanol. The identity of the products obtained by the three methods was confirmed by comparison of their infrared absorption spectra.

Degradation of Sclerotioramine with Alkali or Acid.—When a solution of sclerotioramine (24 g.) in 10% aqueous sodium hydroxide (250 ml.) was heated under reflux in nitrogen for 3 hr., alkaline gas was not evolved. The cooled mixture was acidified with 2N-sulphuric acid, treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate, and distilled until a sample of the distillate was not acidic; the volume of liquid in the distilling flask was maintained by the addition of distilled water as required. After neutralisation with 2N-aqueous sodium hydroxide the distillate was evaporated, leaving colourless salts (8·5 g.), containing sodium acetate which on treatment with *o*-phenylenediamine in the usual manner gave 2-methylbenziminazole (3·3 g.), m. p. and mixed m. p. 172—174°.

The yellow solution formed by heating sclerotioramine (10 g.) with boiling 5N-sulphuric acid (250 ml.) for 32 hr. was decanted from a black solid, treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate to remove carbonyl compounds, and distilled, with the addition of water as required, until the distillate was neutral. Evaporation of the neutralised distillate and treatment of the residual salts (2·7 g.) with *o*-phenylenediamine in the usual manner gave 2-methylbenziminazole (0·1 g.), m. p. and mixed m. p. 174°.

apo*Sclerotioramine*.—When a solution of sclerotioramine (10 g.) in 2N-aqueous sodium hydroxide (150 ml.) was shaken with zinc dust (10 g.) for 15 min. the initial red colour changed to yellow; 5 min. later the mixture was filtered through a plug of glass wool into an excess of 2N-sulphuric acid at about 0°. The precipitated yellow solid was quickly isolated and purified by crystallisation from aqueous alcohol, giving apo*sclerotioramine sulphate* in bright yellow needles (*ca.* 5 g.) which did not melt but slowly decomposed at above 180° [Found: C, 58·8; H, 6·2; N, 3·2; Cl, 10·9. $(C_{19}H_{22}O_2NCl)_2,H_2SO_4$ requires C, 59·8; H, 6·0; N, 3·7; Cl, 9·3%]. The sulphate, which gave a positive test for sulphate ion, readily dissolved in 2N-aqueous sodium hydroxide, giving a yellow solution from which 2N-sulphuric acid reprecipitated the parent salt. 2N-Aqueous sodium hydroxide was added to a suspension of the sulphate (2 g.) in water (15 ml.) until a clear solution was formed. A stream of carbon dioxide then precipitated a brown solid which was collected, washed, and purified from methanol or alcohol, giving apo*sclerotioramine* in pale orange plates (0·8 g.), m. p. 237—238° (decomp.) (Found: C, 67·9; H, 6·6. $C_{19}H_{22}O_2NCl$ requires C, 68·7; H, 6·6%). This compound, which is soluble in the usual organic solvents and does not form a picrate, readily forms a yellow solution in 2N-aqueous sodium hydroxide which does not react with benzenediazonium chloride. Ozonolysis of *apo*-sclerotioramine under a variety of conditions gave (+)-α-methylbutyraldehyde (isolated and characterised as the 2 : 4-dinitrophenylhydrazone) as the only product.

Acidification of a solution of *apo*sclerotioramine (0·2 g.) in 2N-aqueous sodium hydroxide (10 ml.) with 2N-hydrochloric acid gave a bright yellow precipitate of apo*sclerotioramine hydrochloride* which separated from alcohol in yellow-green needles, m. p. 262° (decomp.) (Found: C, 60·3; H, 6·4; N, 3·8; Cl, 18·3. $C_{19}H_{22}O_2NCl,HCl$ requires C, 61·9; H, 6·3; N, 3·8; Cl, 19·3%). Prepared in a similar manner from the free base, the sulphate was identical with that obtained directly in the reduction of sclerotioramine.

Estimation of the Acids Produced by the Reductive Alkaline Degradation of Sclerotioramine.—All reagents employed in the following experiments on evaluations of the amount of acetic acid produced in the decomposition of sclerotioramine with zinc dust and alkali gave negative tests for chloride ions.

Sclerotioramine (23 g.) was reduced with zinc and alkali by the standard procedure and on isolation the solid product was acetylated, giving di-*O*-acetyl*apo*sclerotioramine (12 g.), m. p. and mixed m. p. 154°. The clear, aqueous acidic liquors were distilled from a large flask with an anti-splash device until the distillate was neutral to litmus (3 days); the volume of solution was maintained by intermittent addition of distilled water. A sample of the distillate, which had the smell of acetic acid and did not give a precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate, gave a copious white precipitate with silver nitrate–nitric acid. After neutralisation with aqueous sodium hydroxide (phenolphthalein) the main fraction of the distillate (*ca.* 5 l.) was evaporated on a steam-bath and the residue dried to constant weight (11·8 g.).

From trial experiments it became obvious that the salts contained sodium carbonate and sodium chloride and that the estimation and identification of the acetic acid as 2-methylbenziminazole was to some extent dependent on the concentration of the contaminants.

Consequently a number of comparative blank tests were performed with the object of defining the limits of accuracy of this estimation. The results are listed in the Table.

Na acetate and added salts	Crude yield (g.) and m. p.	Once crystallised yield (g.), m. p.	Twice crystallised yield (g.), m. p.
NaOAc (1 g.)	0·439 166—173°	0·305 170—174°	0·250 174—176°
NaOAc (1 g.) K_2CO_3 (1 g.)	0·364 172—174°	0·218 176—178°	0·126 176—178°
NaOAc (1 g.) Na_2CO_3 (1 g.) NaCl (1 g.)	0·465 150—154°	0·251 174—176°	0·177 175—176°
NaOAc (0·5 g.) Na_2CO_3 (1 g.) NaCl (0·5 g.)	0·60 90—100°	0·124 173—176°	0·080 175—176°

The following conditions were employed. A mixture of sodium acetate (1 g.), *o*-phenylenediamine (1·5 g.), added salts if any, concentrated hydrochloric acid (10 ml.), and distilled water (10 ml.) was heated under reflux for 1 hr., cooled, neutralised with ammonia (*d* 0·88), and cooled to −5°. The product which separated was purified by being twice crystallised from the minimum of hot water. On the basis of the tabulated results the extreme values for the yield of once recrystallised 2-methylbenziminazole from 1 g. of sodium acetate is 0·218—0·305 g. The same conditions were used for the preparation of 2-methylbenziminazole from the mixed sodium salts derived from sclerotioramine and the weight of mixed amounts of contaminants adjusted so that the mixture contained approximately 1 g. of sodium acetate, giving the following results:

Salts (g.)	Crude yield (g.)	Once crystallised yield (g.), m. p.	Twice crystallised yield (g.), m. p.
2·602	0·498	0·253, 176—177°	0·19, 175—176°
2·156	0·390	0·214, 175—177°	0·135, 176—177°

The number of mols. of acetic acid produced per mol. of sclerotioramine was calculated as follows: 1 mol. of sodium acetate being assumed to be produced per mol. of sclerotioramine, the wt. of sodium acetate formed would be 4·81 g. per 23 g. of sclerotioramine. The wt. of sodium acetate in the mixed salts is:

$$\frac{\text{yield of 2-methylbenziminazole from salts}}{\text{yield of 2-methylbenziminazole from 1 g. of NaOAc in standard mixture}} = A$$

Therefore, no. of mol. of sodium acetate formed is:

$$\frac{A\ (\text{total wt. of salts})}{\text{Wt. of salts taken for preparation of 2-methylbenziminazole}} \times \frac{1}{4{\cdot}81}$$

For the product once crystallised the extreme values of 0·78—1·14 mol. of sodium acetate per mol. of sclerotioramine were obtained.

The 2-methylbenziminazole obtained was identical with an authentic specimen [confirmed by conversion into the picrate, m. p. and mixed m. p. 211—213° (decomp.)].

Di-O-acetylaposclerotioramine.—A mixture of *apo*sclerotioramine (0·5 g.), acetic anhydride (10 ml.), and pyridine (6 drops) rapidly became homogeneous and 48 hr. later the solution was poured on ice (50 g.). Purified from alcohol, the solid gave *di-O-acetylaposclerotioramine* in needles (0·5 g.), m. p. 154°, which darkened slowly on being kept, were insoluble in cold 2N-aqueous sodium hydroxide, and had $[\alpha]_D^{20}$ +10·6° [Found: C, 66·7, 66·4; H, 6·3, 6·5; N, 3·4; Cl, 8·8; OAc, 20·5%; *M* (Menzies–Wright), 407, 422. $C_{19}H_{20}NCl(OAc)_2$ requires C, 66·3; H, 6·3; N, 3·4; Cl, 8·5%; *M*, 415·5]. An alcoholic solution of this acetate exhibits an intense violet fluorescence. The same diacetate (13 g.), m. p. and mixed m. p. 153—154°, was obtained when a solution from *apo*sclerotioramine sulphate (from 20 g. of sclerotioramine), acetic anhydride (200 ml.), and pyridine (15 ml.) was kept for 23 hr. and poured into water (500 ml.) with stirring.

When di-*O*-acetyl*apo*sclerotioramine (0·1 g.) was warmed for 1 hr. with 2N-alcoholic sodium hydroxide and the cooled solution acidified with 2N-sulphuric acid an orange precipitate separated which on purification from alcohol gave *apo*sclerotioramine sulphate (0·1 g.) in yellow needles, identical with an authentic specimen. Heating on the steam-bath with methanol (10 ml.) and hydrochloric acid (3 ml.), followed by evaporation of the yellow solution, converted

the diacetate (1 g.) into *di*-O-*acetyl*apo*sclerotioramine hydrochloride*, yellow needles (0·95 g.), m. p. 244—245° [Found: C, 61·1; H, 6·3; Cl, (ionic), 9·0; Cl (total), 17·7. $C_{19}H_{20}NCl(OAc)_2.HCl$ requires C, 61·2; H, 6·0; Cl, (ionic), 8·0; Cl (total), 15·8%].

Dihydrosclerotioramine.—After addition of aqueous ammonia (5 ml.; *d* 0·88) to dihydrosclerotiorin [1] (1 g.) in methanol (20 ml.) the mixture was kept for 20 min. and poured into stirred 2N-sulphuric acid (250 ml.). Purified from methanol, the precipitate gave *dihydrosclerotioramine* in orange needles (0·85 g.), m. p. 171—172° (decomp.) (Found: C, 64·6; H, 7·0; N, 3·4. $C_{21}H_{26}O_4NCl$ requires C, 64·6; H, 6·6; N, 3·6%). This compound is readily soluble in cold 2N-aqueous sodium hydroxide from which it is precipitated unchanged.

Di-O-*acetyldihydro*apo*sclerotioramine*.—A solution of dihydrosclerotioramine (1·6 g.) in 2N-aqueous sodium hydroxide (100 ml.), containing zinc dust (2 g.), was shaken until the originally red solution had become colourless; it was then filtered through glass wool into 2N-sulphuric acid (200 ml.) at 0°. On acetylation by pyridine–acetic anhydride at room temperature for 12 hr., the crude precipitate gave *di*-O-*acetyldihydro*apo*sclerotioramine*, forming needles (0·8 g.) from aqueous alcohol which melted at 70°, resolidified at *ca.* 76°, and then melted at 140—146° (Found: C, 66·0; H, 6·4; N, 3·3; Cl, 9·1; OAc, 20·3; OMe, 0. $C_{23}H_{28}O_4NCl$ requires C, 66·1; H, 6·7; N, 3·4; Cl, 8·5; OAc, 20·60%).

Tetrahydrosclerotioramine.—A solution of sclerotioramine (2 g.) in acetic acid (50 ml.) was hydrogenated with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) and the experiment interrupted after 32 min. when approximately 3 mols. of hydrogen had been absorbed. Purification of the product from aqueous alcohol gave *tetrahydrosclerotioramine* in orange prisms (0·2 g.), m. p. 185° (decomp.) (Found: C, 64·3; H, 7·1; N, 3·5; Cl, 10·1. $C_{21}H_{28}O_4NCl$ requires C, 64·4; H, 7·2; N, 3·6; Cl, 9·0%).

Tetrahydrosclerotiorin (m. p. 143—144°) (0·5 g.) slowly formed an orange-red solution in aqueous ammonia (20 ml.; *d* 0·88) and water (20 ml.), and on acidification with excess of hydrochloric acid this furnished a precipitate which, on purification from aqueous alcohol, gave tetrahydrosclerotioramine in orange prisms (0·3 g.), m. p. and mixed m. p. 186° (decomp.) (Found: C, 63·7; H, 7·1; N, 3·4; Cl, 10·0%). Tetrahydrosclerotioramine, which readily forms orange-red solutions in 2N-aqueous sodium hydrogen carbonate, has a negative ferric reaction in alcohol.

Di-O-*acetyltetrahydro*apo*sclerotioramine*.—(*a*) Reduction of tetrahydrosclerotioramine (0·5 g.) in acetic acid (15 ml.) with zinc dust (1 g.) gave *tetrahydro*apo*sclerotioramine* which separated from alcohol in golden prisms (0·35 g.), m. p. 196° (Found: C, 67·9, 67·6; H, 7·8, 7·8. $C_{19}H_{26}O_2NCl$ requires C, 68·0; H, 7·8%). Prepared by the acetic anhydride–pyridine method at room temperature for 12 hr., *di*-O-*acetyltetrahydro*apo*sclerotioramine* formed needles, m. p. 48°, from alcohol (Found: C, 66·0; H, 7·3. $C_{23}H_{30}O_4NCl$ requires C, 65·8; H, 7·2%).

(*b*) A solution tetrahydrosclerotioramine (1 g.) in acetic acid (50 ml.), containing a palladium–charcoal catalyst (from 1 g. of charcoal and 0·15 g. of palladium chloride), was agitated in hydrogen for 10 hr. Crystallised from alcohol the product gave tetrahydro*apo*sclerotioramine (0·15 g.), m. p. and mixed m. p. 196°. The remainder of the product was an intractable gum.

(*c*) Hydrogenation of tetrahydrosclerotioramine (1 g.) with platinum oxide (50 mg.) in alcohol (100 ml.) during 2 hr. gave tetrahydro*apo*sclerotioramine (0·1 g.), m. p. and mixed m. p. 196°.

Ozonolysis of Di-O-*acetyl*apo*sclerotioramine*.—A slow stream of ozone and oxygen was passed into a solution of the di-*O*-acetate (4 g.) in ethyl acetate at room temperature for 5 hr., the solvent was removed in a vacuum, and water (20 ml.) was added to the residue. Next day the aqueous liquor was decanted and the solid was purified from alcohol and dioxan, giving *di*-O-*acetyl*apo*sclerotaminic* acid in needles (1 g.), m. p. 243—245° (decomp.), $[\alpha]_D^{21}$ 0° [Found: C, 53·6; H, 3·8; N, 4·0; Cl, 10·0; OAc, 25·8; *C*-Me, 13·0. $C_9H_2NCl(Me)(OAc)_2{\cdot}CO_2H$ requires C, 53·4; H, 3·6; N, 4·2; Cl, 10·5; OAc, 25·5; *C*-Me, 13·3%]. This acid is very sparingly soluble in alcohol and dioxan, insoluble in 2N-aqueous sodium carbonate or 2N-hydrochloric acid, and readily soluble in 2N-aqueous sodium hydroxide or in concentrated hydrochloric acid to give a yellow solution. It does not react with Brady's reagent and has a negative ferric reaction in alcohol, but on the addition of a little solid ferrous sulphate gives a bright red colour in this solvent.

The aqueous liquor from the decomposition of the ozonide (from 12 g. of amine) was mixed with an excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate and next day the yellow precipitate was collected, dried, and purified by chromatography from alcohol on neutralised

aluminium oxide, giving (+)-α-methylbutyraldehyde 2 : 4-dinitrophenylhydrazone (0·7 g.), m. p. and mixed m. p. 132°. Admixed with the 2 : 4-dinitrophenylhydrazone of acetone, it had m. p. *ca.* 100°.

Methyl Di-O-acetylaposclerotaminate.—When excess of ethereal diazomethane was added to a suspension of di-*O*-acetyl*apo*sclerotaminic acid (2 g.) in methanol (40 ml.) a clear solution formed in 15 min. After the decomposition of the excess of reagent with acetic acid the solution was evaporated, the residue neutralised with 2N-aqueous sodium hydrogen carbonate, and the precipitate purified from methanol, giving the *methyl di-O-acetylaposclerotaminate* in needles (1·5 g.), m. p. 185° [Found: C, 54·5, 54·3; H, 4·5, 4·2; N, 3·9; Cl, 11·8; OMe, 8·6. 8·5; OAc, 23·6. $C_{11}H_5ONCl(OMe)(OAc)_3$ requires C, 54·4; H, 4·0; N, 4·0; Cl, 10·1; OMe, 8·8; OAc, 24·5%]. This ester has a negative ferric or ferrous sulphate reaction in alcohol and is insoluble in 2N-aqueous sodium hydroxide. Chromatography of this ester from methanol on neutralised alumina gave *methyl O-acetylaposclerotaminate*, forming almost colourless needles, m. p. 213—216° (decomp.), from methanol [Found: C, 54·9; H, 4·5; N, 4·5; Cl, 11·5; OAc, 13·8. $C_{13}H_9O_3NCl(OAc)$ requires C, 54·3; H, 3·9; N, 4·5; Cl, 11·4; OAc, 13·9%]. The same monoacetate of the ester (with an identical infrared absorption spectrum) separated when the parent methyl di-*O*-acetyl*apo*sclerotaminate was allowed to crystallise slowly from much aqueous methanol during 1—2 weeks. Admixed with the diacetate of the ester it had m. p. *ca.* 166—190° (decomp.) and on acetylation with pyridine–acetic anhydride at room temperature for 46 hr. quantitatively regenerated the diacetate of the methyl ester, forming needles, m. p. and mixed m. p. 182°, from methanol.

Aqueous ammonia solution (13 ml.; *d* 0·88) was added to di-*O*-acetyl*apo*sclerotaminic acid (1 g.) suspended in warm alcohol (15 ml.), and the resultant pale brown solution evaporated in a vacuum to a volume of *ca.* 5 ml. On being kept at 0° overnight, this deposited a semicrystalline ammonium salt (0·45 g.) which on dissolution in acetic acid (2 ml.) gave O-*acetyl*apo*sclerotaminic acid* in fawn-coloured prisms (0·4 g.), m. p. 280° (decomp.) with darkening from 230° [Found: C, 50·6; H, 4·0; N, 4·1; Cl, 11·1; OAc, 17·0. $C_{11}H_7O_3NCl(OAc),H_2O$ requires C, 50·0; H, 3·8; N, 4·5: Cl, 11·30; OAc, 13·7%].

Methyl apo*Sclerotaminate.*—A solution of di-*O*-acetyl*apo*sclerotaminic acid (2 g.) in methanol (200 ml.) and concentrated hydrochloric acid (10 ml.) was evaporated on the steam-bath to 50 ml., mixed with methanol (140 ml.) and concentrated hydrochloric acid (10 ml.), and again evaporated to 50 ml. Next day the crystalline product was purified from methanol, furnishing *methyl* apo*sclerotaminate* in yellow needles (1·2 g.), m. p. 244—245° (decomp.), insoluble in cold 2N-aqueous sodium hydroxide or in hot water [Found: N, 4·6; OMe, 9·9. $C_{11}H_7O_3NCl{\cdot}OMe$ requires N, 5·3; OMe, 11·6%]. Acetylation of this ester with pyridine–acetic anhydride at room temperature gave methyl di-*O*-acetyl*apo*sclerotaminate in needles, m. p. and mixed m. p. 185°, further identified by comparison of the infrared spectra (Found: C, 54·6; H, 4·1; N, 3·9. Calc. for $C_{16}H_{14}O_6NCl$: C, 54·4; H, 4·0; N, 4·0%).

A solution of di-*O*-acetyl*apo*sclerotaminic acid (0·5 g.) in 5% methanolic potassium hydroxide (20 ml.) was heated under reflux for 1 hr., cooled, and saturated with hydrogen chloride at 0°. After the removal of the inorganic salts the solution was concentrated to yield methyl *apo*sclerotaminate (0·25 g.) which separated from methanol in yellow needles, m. p. and mixed m. p. 245° (decomp.), having the requisite infrared spectrum.

apo*Sclerotaminic Acid.*—A solution of di-*O*-acetyl*apo*sclerotaminic acid (1·1 g.) in 2N-aqueous sodium hydroxide (75 ml.) was warmed on the steam-bath for 1 hr., cooled, and acidified with hydrochloric acid. Next day the semicrystalline product was collected and purified from methanol or dioxan, giving *apo*sclerotaminic acid in yellow needles, m. p. >300°, readily soluble in 2N-aqueous sodium hydrogen carbonate. By pyridine–acetic anhydride this was converted quantitatively into di-*O*-acetyl*apo*sclerotaminic acid, m. p. and mixed m. p. 242—243° (decomp.).

Methylation of Methyl apo*Sclerotaminate.*—Methylation of this ester (1·5 g.) (or of *apo*sclerotaminic acid, 0·5 g.) with methyl iodide (4 ml.) and potassium carbonate (5 g.) in boiling acetone (20 ml.) for 4 hr. gave *methyl* NO-*dimethyl*apo*sclerotaminate* which, on repeated purification from methanol, formed yellow needles (0·1 g.), m. p. 224° [Found: C, 57·1; H, 5·2; OMe, 21·2. $C_{13}H_9O_2NCl(OMe)_2$ requires C, 56·9; H, 4·7; OMe, 21·0%]. Dilution of the methanolic mother-liquors with water furnished a semi-crystalline product which on repeated purification from methanol furnished *methyl di-O-methylaposclerotaminate* in needles (0·25 g.), m. p. 168° [Found: C, 56·9; H, 4·5; N, 4·7; Cl, 12·0; OMe, 30·8. $C_{11}H_5ONCl(OMe)_3$ requires C, 56·9; H, 4·7; N, 4·7; Cl, 11·7; OMe, 31·5%].

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NO-*Dimethyl*apo*sclerotioramine*.—Methylation of *apo*sclerotioramine sulphate (1 g.) with potassium carbonate (5 g.) and methyl iodide (4 ml.) in boiling acetone (25 ml.) for 1 hr. gave a gum which was purified by chromatography from benzene on neutralised aluminium oxide. After elution with benzene had removed a dark band from the column, elution with methanol gave NO-*dimethyl*apo*sclerotioramine* which formed yellow needles (0·1 g.), m. p. 246° (decomp.), from methanol [Found: C, 70·8; H, 7·2; N, 3·8; OMe, 8·6. $C_{19}H_{20}OCl(OMe)(NMe)$ requires C, 70·2; H, 7·1; N, 3·8; OMe, 8·6%].

NOO-*Trimethyl*apo*sclerotioramine Methosulphate*.—Methylation of *apo*sclerotioramine sulphate (2 g.) with potassium carbonate (5 g.) and methyl sulphate (2 g.) in boiling acetone (150 ml.) for 20 min. gave NOO-*trimethyl*apo*sclerotioramine methosulphate* which separated from benzene in pale yellow needles (1·2 g.), m. p. 212° (decomp.) [Found: C, 57·2; H, 6·5; N, 2·8; Cl, 7·2; OMe, 17·2. $C_{19}H_{20}Cl(NMe)(OMe)_2,MeSO_4$ requires C, 57·0; H, 6·6; N, 2·9; Cl, 7·3; OMe, 19·2%]; this product gives a positive test for sulphur.

*Ozonolysis of Di-*O*-benzoyl*apo*sclerotioramine*.—Benzoyl chloride (10 ml.) was added gradually to a well shaken solution of *apo*sclerotioramine (4·8 g.) in pyridine (20 ml.) at 0°, and the mixture was kept at room temperature for 4 hr., then poured into ice-water (150 g.). Purified from methanol–benzene, the product gave *di*-O-*benzoyl*apo*sclerotioramine* in needles (3·8 g.), m. p. 181°, $[\alpha]_D^{21}$ +19·3°, insoluble in 2N-aqueous sodium hydroxide or 2N-hydrochloric acid (Found: C, 73·7, 73·2; H, 5·7, 5·7; N, 2·5; Cl, 6·8, 6·8. $C_{33}H_{30}O_4NCl$ requires C, 73·4: H, 5·6; N, 2·6; Cl, 6·6%).

A stream of ozone and oxygen was passed into a solution of this dibenzoate (2·3 g.) in ethyl acetate (150 ml.) for 4 hr., the solvent was removed in a vacuum, and water (25 ml.) was added to the residue. Purification of the resulting solid from alcohol gave *di*-O-*benzoyl*apo*sclerotaminic acid*, m. p. 212—214° (decomp.) (Found: Cl, 8·1; *C*-Me, 0·9. $C_{25}H_{16}O_6NCl$ requires Cl, 7·7; *C*-Me, 3·1%).

*Ozonolysis of the Di-*O*-toluene-*p*-sulphonate of* apo*Sclerotioramine*.—Toluene-*p*-sulphonyl chloride (40 g.) was added to a solution of *apo*sclerotioramine sulphate (15 g.) in pyridine (100 ml.) at 0° and ½ hr. later the mixture was heated on the steam-bath for 15 min. and then poured, with stirring, into water. Repeated crystallisation of the solid from ethanol and then benzene–methanol gave the *di*-O-*toluene*-p-*sulphonate* of *apo*sclerotioramine in needles (12 g.), m. p. 153°, $[\alpha]_D^{21}$ +33°, readily forming a yellow solution in concentrated hydrochloric acid from which it was precipitated unchanged on dilution with water (Found: C, 62·1; H, 5·9; N, 2·0; Cl, 5·7. $C_{33}H_{34}O_6NClS_2$ requires C, 62·0; H, 5·4; N, 2·2; Cl, 5·5%).

A stream of ozone and oxygen was passed into a solution of this di-*O*-toluene-*p*-sulphonate (2 g.) in ethyl acetate (150 ml.) at room temperature for 4 hr. Decomposition of the ozonide with water (20 ml.) for 12 hr. followed by purification of the product from alcohol gave the *di*-O-*toluene*-p-*sulphonate* of *apo*sclerotaminic acid in plates (0·6 g.), m. p. 217° (decomp.), $[\alpha]_D^{22}$ 0° (Found: C, 53·3, 53·6, 53·5; H, 4·2, 3·9, 3·8; N, 2·5; Cl, 6·0, 6·0. $C_{25}H_{20}NClO_8S_2$ requires C, 53·4; H, 3·6; N, 2·5; Cl, 6·5%). The aqueous solution from the decomposition of the ozonide furnished (+)-α-methylbutyraldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 129°.

The foregoing acid (2 g.) suspended in methanol (50 ml.) was esterified with diazomethane, and the excess of reagent decomposed with acetic acid. After the removal of a little acidic material with 2N-aqueous sodium hydrogen carbonate the resulting *methyl ester* separated from methanol in prisms (1·4 g.), m. p. 158° (Found: C, 54·0, 54·6; H, 4·0, 4·0; N, 2·5; Cl, 5·7; OMe, 5·2. $C_{25}H_{19}NClO_7S_2$·OMe requires C, 54·2; H, 3·5; N, 2·4; Cl, 6·2; OMe, 5·4%). When this ester was heated with Raney nickel (W.4 grade) in boiling methanol the only product recovered was varying amounts of unchanged starting material.

A solution of di-*O*-toluene-*p*-sulphonate (1·2 g.) of *apo*sclerotaminic acid in methanol (50 ml.) containing Raney nickel (6 g. of W.4 grade) was boiled for 3 hr., filtered, and evaporated, leaving a pale green solid (0·5 g.). Purification of this by chromatography from benzene on neutralised aluminium oxide furnished a *complex* which separated from benzene in pale green needles (0·2 g.), m. p. >300°, insoluble in 2N-aqueous sodium hydroxide or 2N-hydrochloric acid, containing nickel and giving a positive test for sulphur [Found: C, 50·6; H, 3·8; N, 3·1; Cl, 6·7. $(C_{25}H_{19}NClO_8S_2)_2Ni$ requires C, 50·9; H, 3·2; N, 2·4; Cl, 6·0%].

*N-Methyl*iso*sclerotioramine*.—Addition of water to the dark violet solution formed by adding 2N-aqueous sodium hydroxide (5 ml.) to *N*-methylsclerotioramine (1 g.), dissolved in the minimum volume of alcohol, gave a violet precipitate which on purification from aqueous

methanol furnished N-*methyl*iso*sclerotioramine* in violet needles (0·5 g.), m. p. 120—125° (decomp.) (Found: C, 66·2; H, 6·8; N, 3·6; Cl, 9·3. $C_{22}H_{26}O_4NCl$ requires C, 65·4; H, 6·5; N, 3·5; Cl, 8·8%). When *N*-methylsclerotioramine was boiled with 30% sodium aqueous hydroxide solution for 3 days or with 50% sulphuric acid for 2 days, extensive decomposition occurred, but methylamine was not liberated.

NO-*Dimethylsclerotioramine* (with H. Page).—Methyl sulphate (2·5 ml.) was added gradually in 10 min. to an agitated solution of sclerotioramine (1 g.) in 2N-aqueous sodium hydroxide (50 ml.) at 0° and 15 min. later a deep red oil (which became solid 24 hr. later at −5°) separated from the alkaline solution. Purification of this solid by chromatography from methanol on neutral aluminium oxide furnished NO-*dimethylsclerotioramine* in purple plates (0·1 g.), m. p. 223° [Found: C, 66·5, 66·4; H, 6·9, 6·8; N, 3·7, 3·4; Cl, 8·9; OMe, 8·3, 8·0; *N*-Me, 6·0. $C_{21}H_{22}O_3Cl(NMe)(OMe)$ requires C, 66·1; H, 6·7; N, 3·4; Cl, 8·5; OMe, 7·4; *N*-Me, 7·0%]. Numerous variations of the reaction conditions failed to increase the yield of this product. Methylated by the same method, *N*-methylsclerotioramine (1 g.) gave *NO*-dimethylsclerotioramine, forming purple plates (0·15 g.) from methanol, m. p. and mixed m. p. 218°.

Tetrahydro-NO-*dimethylsclerotioramine*.—On dropwise addition of methyl sulphate (2 ml.) to a vigorously agitated solution of tetrahydrosclerotioramine (1 g.) in 2N-aqueous sodium hydroxide (50 ml.) at 0° in 10 min. an orange oil separated which solidified at 0° in 48 hr. and was then purified by chromatography from alcohol on neutral aluminium oxide, giving *tetrahydro*-NO-*dimethylsclerotioramine*. This crystallised from alcohol in orange-red plates (0·25 g.), m. p. 188° (Found: C, 66·1; H, 7·9; OMe, 8·0. $C_{22}H_{29}O_3NCl{\cdot}OMe$ requires C, 65·6; H, 7·7; OMe, 7·4%).

N-*Methyl*apo*sclerotioramine*.—Sufficient alcohol was added to *N*-methylsclerotioramine (2 g.) suspended in 2N-aqueous sodium hydroxide (10 ml.) to form a solution. Zinc dust (3 g.) was then introduced and the mixture shaken for about 10 min., until the initial purple colour changed to pale yellow, and then filtered into an excess of 2N-sulphuric acid at 0°. The dried precipitate was acetylated by pyridine–acetic anhydride at room temperature, giving O-*acetyl*-N-*methyl*apo*sclerotioramine* which separated from alcohol in pale yellow needles (1 g.), m. p. 230° (Found: C, 67·0; H, 6·7; N, 3·5; Cl, 9·4. $C_{22}H_{26}O_3NCl$ requires C, 67·0; H, 6·7; N, 3·6; Cl, 9·2%). The following method was somewhat more convenient for this preparation. On the addition of zinc dust (3 g.) to an agitated solution of *N*-methylsclerotioramine (2 g.) in acetic acid (25 ml.) the colour changed from red to pale yellow in 5 min. and the mixture was then filtered into ice-water. Purification of the yellow precipitate from aqueous alcohol gave N-*methyl*apo*sclerotioramine* in yellow needles (1·6 g.), m. p. 230—235° (decomp.) (Found: C, 68·7; H, 6·0; N, 3·4. $C_{20}H_{24}O_2NCl$ requires C, 69·5; H, 6·9; N, 4·1%). Acetylation of this with pyridine–acetic anhydride at room temperature furnished *O*-acetyl-*N*-methyl-*apo*sclerotioramine in pale yellow needles (1·5 g.), m. p. and mixed m. p. 229° (Found: C, 67·1; H, 6·7; N, 3·3; OAc, 13·7. Calc. for $C_{20}H_{23}ONCl{\cdot}OAc$: C, 67·0; H, 6·7; N, 3·6; OAc, 1·2%).

Reduction of *NO*-dimethylsclerotioramine with zinc and acetic acid or with zinc and alkali gave rise to *N*-methyl*apo*sclerotioramine, m. p. and mixed m. p. 230—235° (decomp.), giving the *O*-acetyl derivative, m. p. and mixed m. p. 229°. The compound and its acetate had the respective authentic infrared absorption spectra.

Distillation of the aqueous liquors remaining after the degradation of *NO*-dimethylsclerotioramine (0·2 g.) with boiling 2N-aqueous sodium hydroxide solution (10 ml.) for ½ hr., followed by acidification of the cooled solution and separation of the precipitate, furnished 2 : 4-dimethylhexa-2-enaldehyde, identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159°.

Methylation of *N*-methyl*apo*sclerotioramine (0·5 g.) by the methyl iodide–potassium carbonate method in boiling acetone gave a mixed product which was purified by chromatography from benzene–ether (1 : 1) on neutralised aluminium oxide. Washed with methanol, a deep red band (*a*) and then a yellow band (*b*) were eluted. Concentration of the eluate (*b*) gave *NO*-dimethyl*apo*sclerotioramine, forming yellow needles (0·25 g.), m. p. and mixed m. p. 250° (decomp.), from methanol, with the expected infrared spectrum. Crystallised from aqueous methanol, the eluate (*a*) furnished violet needles (*ca.* 20 mg.), m. p. 91°, which appeared to be a methiodide. Methylation of *N*-methyl*apo*sclerotioramine (0·5 g.) by the methyl sulphate–potassium carbonate method in boiling acetone gave *NO*-dimethyl*apo*sclerotioramine methosulphate which separated from benzene–methanol in pale yellow needles (0·3 g.),

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m. p. and mixed m. p. 210° (decomp.) (Found: C, 57·3; H, 6·2; N, 2·9. Calc. for $C_{23}H_{32}O_6NClS$: C, 57·0; H, 6·6; N, 2·9%), having the requisite infrared absorption spectra.

Tetrahydro-N-methylsclerotioramine.—Treated with 30% aqueous methylamine (2·5 ml.), tetrahydrosclerotiorin (1 g.) in alcohol (10 ml.) rapidly formed a deep orange solution which gradually deposited crystalline *tetrahydro-N-methylsclerotioramine*. Purified from alcohol, this base formed orange plates (0·8 g.), m. p. 206° (Found: C, 64·7; H, 7·2; Cl, 8·9; N, 3·4. $C_{22}H_{30}O_4NCl$ requires C, 64·8; H, 7·4; Cl, 8·7; N, 3·4%).

O - *Acetyltetrahydro* - N - *methyl*aposclerotioramine.—Tetrahydro - *N* - methylsclerotioramine (0·5 g.), dissolved in acetic acid (5 ml.), was reduced by zinc dust (1 g.) in 10 min. and the mixture filtered into ice-water, giving tetrahydro-*N*-methyl*apo*sclerotioramine which separated from alcohol in pale yellow needles (0·3 g.), m. p. 182° (decomp.). This compound, which contained varying amounts of water of crystallisation, did not give satisfactory analytical results and on acetylation gave O-*acetyltetrahydro*-N-*methyl*aposclerotioramine, forming needles (0·25 g.), m. p. 126°, from alcohol (Found: C, 67·5; H, 7·8. $C_{22}H_{30}O_5NCl$ requires C, 67·4; H, 7·7%).

Reduction of tetrahydro-*NO*-dimethylsclerotioramine (0·5 g.) by the same method gave tetrahydro-*N*-methyl*apo*sclerotioramine (0·4 g.), m. p. and mixed m. p. 182°, forming the monoacetate, m. p. 126°.

Tetrahydro-N-phenylsclerotioramine (with Adelaide Harris).—A solution of *N*-phenylsclerotioramine (1 g.) in alcohol (200 ml.) containing a catalyst (from 0·7 g. of charcoal and 0·25 g. of palladium chloride) was shaken in hydrogen until (100 ml., 2·1 mols.) of gas had been absorbed. Purified from alcohol, the resulting *tetrahydro-N-phenylsclerotioramine* formed orange needles (0·8 g.), m. p. 180°, which on admixture with *N*-phenylsclerotioramine had m. p. 160—162° (Found: C, 69·4; H, 6·8; N, 3·0. $C_{27}H_{32}O_4NCl$ requires C, 69·1; H, 6·8; N, 3·0%). The same compound (0·9 g.), m. p. and mixed m. p. 180°, was prepared from tetrahydrosclerotiorin (1 g.) and aniline (0·5 g.) in alcohol (10 ml.) at room temperature for 48 hr. (Found: C, 68·9; H, 6·9; N, 2·8; Cl, 7·4%).

*Tetrahydro-N-phenyl*aposclerotioramine.—Reduction of tetrahydro-*N*-phenylsclerotioramine (0·5 g.) in acetic acid (10 ml.) with zinc dust (1 g.) was complete in 2 mins., yielding *tetrahydro-N-phenyl*aposclerotioramine which formed yellow plates (0·4 g.), m. p. 256° (decomp.) with darkening from 246°, from alcohol (Found: C, 72·6; H, 7·0. $C_{25}H_{30}O_5NCl$ requires C, 72·6; H, 7·3%). Prepared by the acetic anhydride–pyridine method, O-*acetyltetrahydro-N-phenyl*aposclerotioramine separated from alcohol in needles, m. p. 198° (Found: C, 71·4; H, 7·1. $C_{27}H_{32}O_5NCl$ requires C, 71·4; H, 7·3%).

Dihydro-NO-dimethylsclerotioramine.—Treatment of dihydrosclerotioramine (0·5 g.) in 2N-aqueous sodium hydroxide at 0° with methyl sulphate (2 ml., added dropwise) gave *dihydro-NO-dimethylsclerotioramine* which was purified by chromatography from methanol on neutralised aluminium oxide, followed by crystallisation from the same solvent, forming deep orange needles (0·1 g.), m. p. 166° (Found: C, 66·8; H, 7·7. $C_{23}H_{30}O_4NCl$ requires C, 65·9; H, 7·2%).

Dihydro-N-methylsclerotioramine.—Methylation of dihydrosclerotioramine (0·4 g.) in boiling acetone (15 ml.) with potassium carbonate (4 g.) and methyl iodide (2 ml.) for 2½ hr. gave *dihydro-N-methylsclerotioramine* which separated from methanol in orange plates (0·4 g.), m. p. 219—220 (decomp.) (Found: C, 65·2, 64·9; H, 7·1, 7·2; N, 3·4, 3·3; Cl, 9·2, 9·1; OMe, 0·2; *N*-Me, 9·2. $C_{21}H_{25}O_4ClNMe$ requires C, 65·1; H, 6·9; N, 3·5; Cl, 8·8; *N*-Me, 7·2%). This compound (0·4 g.), m. p. and mixed m. p. 220° (decomp.), was also obtained by the interaction of dihydrosclerotiorin (0·5 g.) and 30% aqueous methylamine (2 ml.).

The ultraviolet absorption spectra were measured in 95% alcohol with a Unicam S.P. 500 Spectrophotometer, and the infrared spectral data were obtained in Nujol on a Grubb-Parsons S.3. double-beam spectrophotometer. The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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989. *Picrotoxin. Part VI.* Picrotoxic Acid and its Derivatives.*

By P. I. Burkhill, J. S. E. Holker, Alexander Robertson, and J. H. Taylor.

Reduction of methyl picrotoxate with potassium borohydride gave a compound, $C_{16}H_{22}O_7$, and, from an examination of this compound and its transformation products in conjunction with the properties of picrotoxic acid and its derivatives, the structure (III; R = H) has been deduced for the latter acid. It is shown that the formation of picrotoxic acid from picrotoxinin can be explained rationally on the basis of the stereochemical description by Conroy [1] of β-bromopicrotoxininic acid with the further assumption that picrotoxinin has the same relative stereochemistry. This work adequately supports the elegant structural deductions of Conroy.

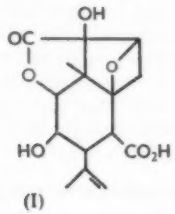
In continuation of our investigations on picrotoxinin and its transformation products (cf. Part V*) some reactions of picrotoxic acid and its derivatives have been studied. This monobasic acid, the methyl ester, and methyl *O*-methylpicrotoxate have been prepared directly from picrotoxinin. Horrmann [2] obtained picrotoxic acid by hydrolysis of picrotoxinin with dilute sulphuric acid, and methyl picrotoxate by treatment of picrotoxinin with potassium hydroxide or sodium methoxide in methanol. The application of the latter reagent has also been studied by Benstead *et al.*[3] who emphasised that in the methanolysis the nature of the product was in the main determined by the concentration of the sodium methoxide; thus with relatively large amounts of the reagent methyl picrotoxate was the only product, but when catalytic amounts were employed methyl picrotoxinindicarboxylate was the major component of the reaction mixture. In our hands the use of a catalytic amount of methoxide invariably produced methyl picrotoxate and methyl picrotoxinindicarboxylate in approximately equal proportions. Methyl *O*-methylpicrotoxate is formed by the action of ethereal diazomethane containing a trace of aqueous potassium hydroxide [3,4] on picrotoxinin but in the absence of alkali methyl picrotoxinindicarboxylate is also produced.[3] By analogous hydrolytic methods dihydropicrotoxinin is converted into dihydropicrotoxic acid or its methyl ester,[3] identical with the products obtained by hydrogenation of picrotoxic acid and methyl picrotoxate respectively. Methyl picrotoxate and dihydropicrotoxate give monoacetates with acetic anhydride–pyridine, monomethyl ethers with diazomethane or methyl sulphate [3] and alkali, and dimethyl ethers by the methyl iodide–silver oxide method.[5] The infrared absorption spectrum of methyl di-*O*-methylpicrotoxate does not show hydroxyl absorption and it therefore appears that methyl picrotoxate contains two hydroxyl groups of which one is sufficiently acidic to be methylated with diazomethane. Further, methyl picrotoxate and its dihydroderivative are immediately soluble in cold dilute aqueous sodium hydroxide and are precipitated unchanged on acidification, a property which has been utilised to separate methyl picrotoxate from non-acidic methyl picrotoxinindicarboxylate formed in the methanolysis of picrotoxinin. The acidity of methyl picrotoxate is attributed to a hydroxyl group rather than to the opening of a lactone ring with alkali because methyl *O*-methylpicrotoxate is insoluble in alkali. Dihydropicrotoxic acid is stable to sodium dichromate in dilute sulphuric acid at 100°, to evaporation with concentrated nitric acid,[3] or to lead tetra-acetate and it therefore appears that both the hydroxyl groups in picrotoxic and dihydropicrotoxic acid are tertiary, and are not present in an α-glycol system. As in the methylation, the ease of acetylation of a tertiary hydroxyl group in methyl picrotoxate

* Part V, *J.*, 1957, 3746.

[1] Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 1726.
[2] Horrmann, *Annalen*, 1916, **411**, 273.
[3] Benstead, Gee, Johns, Martin-Smith, and Slater, *J.*, 1952, 2292.
[4] Sutter and Schlittler, *Helv. Chim. Acta*, 1950, **33**, 902.
[5] Mercer and Robertson, *J.*, 1936, 288.

is attributed to the acidic nature of the group affected and accordingly the resulting monoacetate is insoluble in alkali.

The formula (I) proposed for picrotoxic acid by Benstead *et al.*[3] on the basis of Conroy's structure [6] (II) for picrotoxinin contains a secondary hydroxyl group and consequently is not in agreement with the observed stability of dihydropicrotoxic acid towards oxidising agents.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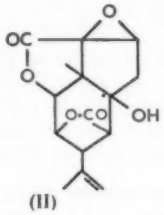
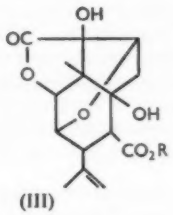
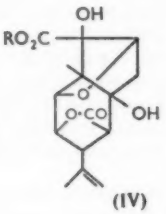
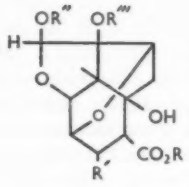
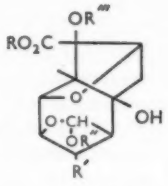

(II)

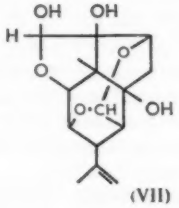

(III)

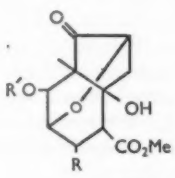

(IV)

On the assumption that the structure (II) for picrotoxinin has the correct carbon skeleton and placement of oxygen functions and that both hydroxyl groups of picrotoxic acid are tertiary, two possible formulations, (III and IV; R = H), may be devised for this compound. It should be noted that on either of these formulations methyl picrotoxate (III or IV; R = Me) would contain an α-hydroxy-ester system [*i.e.*, α-hydroxy-lactone in (III; R = Me)] in which the hydroxyl group would be expected to have acidic properties.[7,8] In an attempt to differentiate between the structures (III and IV; R = Me) methyl picrotoxate was reduced with potassium borohydride, giving a product, $C_{16}H_{22}O_7$, which contained two more hydrogen atoms than the starting material and has been named methyl picrotoxolate. Comparison of the infrared absorption spectra of this compound and of methyl picrotoxate (in mineral oil mull) indicated that although both spectra had peaks at 1745 (methyl ester) and 1650 cm.$^{-1}$ (double bond of the *iso*propenyl system), the


(V)


(VI)


(VII)


(VIII)

band at 1802 cm.$^{-1}$, present in the spectrum of methyl picrotoxate and attributed to a γ-lactone system, was absent from the spectrum of methyl picrotoxolate and it therefore seems probable that the formation of methyl picrotoxolate involves the reduction of a lactone ring to a hemiacetal system. In agreement with this hypothesis methyl picrotoxolate readily regenerated methyl picrotoxate on oxidation with sodium dichromate in dilute sulphuric acid and thus on the basis of the alternative structures (III or IV; R = Me) methyl picrotoxolate would be represented by (V or VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H). The latter ester, the solubility of which in dilute aqueous sodium hydroxide is attributed to the presence of an acidic hydroxyl group of a hemiacetal system, gave a diacetate (V or VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = Ac) and on treatment with methanolic hydrogen chloride or methyl sulphate and alkali a monomethyl ether,

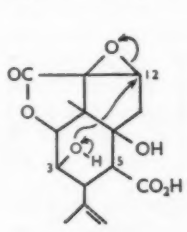
[6] Conroy, *J. Amer. Chem. Soc.*, 1952, **74**, 491, 3046.
[7] Benstead, Brewerton, Fletcher, Martin-Smith, Slater, and Wilson, *J.*, 1952, 1042.
[8] Schmidt *et al.*, reported by Eistert in "Newer Methods of Preparative Organic Chemistry," Interscience, London, 1948, p. 520; *Ber.*, 1934, **67**, 2120, 2127.

methyl *O*-methylpicrotoxolate formulated as the acetal (V or VI; R = R″ = Me, R′ = ·CMe:CH_2, R‴ = H) which formed a monoacetate (V or VI; R = R″ = Me, R′ = ·CMe:CH_2, R‴ = Ac) and on alkaline hydrolysis gave rise to *O*-methylpicrotoxolic acid (V or VI; R = R‴ = H, R′ = ·CMe:CH_2, R″ = Me).

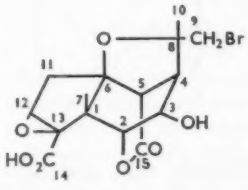
On hydrogenation methyl picrotoxolate gave methyl dihydropicrotoxolate (V or VI; R = Me, R′ = $CHMe_2$, R″ = R‴ = H), which was identical with the product obtained by reduction of methyl dihydropicrotoxate with potassium borohydride. This dihydro-derivative regenerated methyl dihydropicrotoxate on oxidation with sodium dichromate in dilute sulphuric acid, and, like methyl picrotoxolate, formed a diacetate (V or VI; R = Me, R′ = $CHMe_2$, R″ = R‴ = Ac).

Of the two alternative possible structures for methyl picrotoxolate, formula (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) contains an α-hydroxy-hemiacetal system in the same environment as that in compound A (VII) derived by the reduction of picrotoxinin with lithium aluminium hydride [9] and it was therefore possible to differentiate between structures (V and VI; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) for methyl picrotoxolate by reactions similar to those described in the elucidation of the structure of compound A.[9] Thus methyl picrotoxolate consumed one mol. of sodium metaperiodate rapidly, yielding a formate, $C_{16}H_{20}O_7$, the nature of which was established by hydrolysis with dilute sulphuric acid to the alcohol, $C_{15}H_{20}O_6$, which on subsequent formylation regenerated the parent ester. These products are strictly analogous to the compounds obtained from compound A by similar reactions, indicating that methyl picrotoxolate contains an α-hydroxy-hemiacetal system and therefore must be represented by structure (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H). Accordingly, the sodium metaperiodate product and the derived alcohol are formulated as (VIII; R = ·CMe:CH_2, R′ = ·CHO) and (VIII; R = ·CMe:CH_2, R′ = H) respectively. In agreement with the structure (VIII; R = ·CMe:CH_2, R′ = H) this compound, which did not react with lead tetra-acetate, formed a monoacetate (VIII; R = ·CMe:CH_2, R′ = Ac) and a yellow 2 : 4-dinitrophenylhydrazone. Strictly analogous properties were exhibited by methyl dihydropicrotoxolate. Thus, on treatment with sodium metaperiodate this ester gave the keto-formate (VIII; R = $CHMe_2$, R′ = CHO) which with cold dilute sulphuric acid generated the corresponding keto-alcohol (VIII; R = $CHMe_2$, R′ = H), and this product gave a monoacetate (VIII; R = $CHMe_2$, R′ = Ac] with acetic anhydride—pyridine, formed a 2 : 4-dinitrophenylhydrazone, and with formic acid and acetic anhydride regenerated the parent keto-formate.

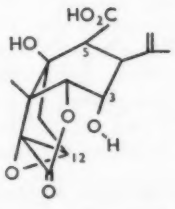
These results provide cogent evidence in favour of the structures (V; R = Me, R′ = ·CMe:CH_2, R″ = R‴ = H) and (V; R = Me, R′ = $CHMe_2$, R″ = R‴ = H) for methyl picrotoxolate and its dihydro-derivative respectively and hence picrotoxic acid may be represented by formula (III; R = H).



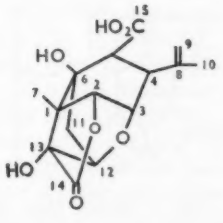
(IX)



(X)



(XI)



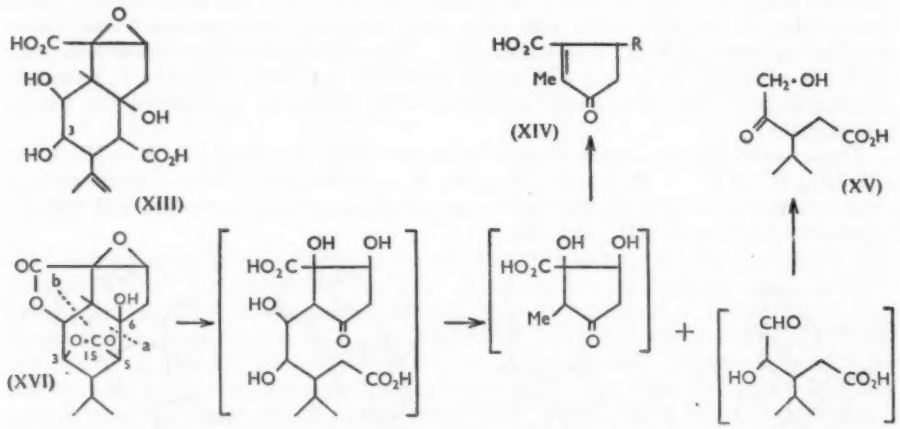
(XII)

In the conversion of picrotoxinin (II) into picrotoxic acid (III; R = H) by hydrolysis it is assumed that the lactone ring bridging $C_{(3)}$ and $C_{(5)}$ is opened and that the 3-hydroxyl

[9] Holker, Holker, McGookin, Robertson, and Sargeant, *J.*, 1957, 3746.

group thus generated is spatially situated in a suitable position for rearward attack at $C_{(12)}$ of the epoxide ring by an internal S_N2 mechanism (expression IX). In a recent publication [1] Conroy has considered the properties of β-bromopicrotoxininic acid and related compounds and on the basis of the original structure (II) for picrotoxinin has derived the stereochemical formulation (X) for this acid. If it is assumed that picrotoxinin has the same relative stereochemical description, it becomes apparent that, when the lactone ring bridging $C_{(3)}$ and $C_{(5)}$ in picrotoxinin is opened, the *cyclo*hexane ring is no longer rigid and can take up the conformation shown in (XI) in which the 3-hydroxyl group is situated in an ideal position for reaction with the epoxide ring as postulated above. Thus, on this basis picrotoxic acid has the stereochemical description (XII) and the mechanism of its formation adequately supports the deductions of Conroy. It should be noted that on the basis of formula (XIII) for picrotoxinindicarboxylic acid proposed by Conroy [6] the 3-hydroxyl group should similarly be in an ideal position for rearward attack on the epoxide ring, and hence this acid should be readily isomerised. This problem is at present under investigation.

Picrotoxinin and α-picrotoxininic acid react with bromine to give insoluble saturated monobromo-derivatives, containing a β-bromo-ether system [2,10] of the type illustrated in structure (X) for β-bromopicrotoxininic acid. Conroy [1] has indicated that in the formation of compounds of this type it is necessary to assume that the tertiary 6-hydroxyl group is within bonding distance of the *iso*propenyl group in picrotoxinin and in α-picrotoxininic acid. Picrotoxic acid and its derivatives do not form monobromo-derivatives and Benstead *et al.*[3] originally proposed structure (I) for picrotoxic acid in an attempt to explain this anomaly. It is now clear from structure (XII) for picrotoxic acid that in the formation of an ether link between $C_{(3)}$ and $C_{(12)}$, the *cyclo*hexane ring has adopted a rigid conformation in which the tertiary 6-hydroxyl group and the 4-*iso*propenyl group are too far apart to take part in the formation of a 6 : 8-ether link. Accordingly, on this basis, picrotoxic acid and its derivatives would not be expected to form monobromo-substitution products.

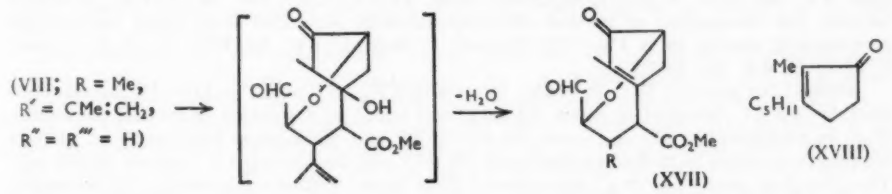


It is known that picrotoxinin, α-picrotoxininic acid, and their respective dihydro-derivatives are degraded by treatment with alkali under very mild conditions. Thus, Sutter and Schlittler [11] have isolated compounds (XIV; R = H), (XIV; R = OH), and (XV) by degradation of α-dihydropicrotoxinin (XVI) with sodium carbonate. On the other hand, picrotoxic acid, picrotoxinindicarboxylic acid, their respective dihydro-

[10] O'Donnel, Robertson, and Harland, *J.*, 1939, 1261.
[11] Sutter and Schlittler, *Helv. Chim. Acta*, 1949, **32**, 1855.

derivatives and methyl esters, as well as β-bromopicrotoxininic acid and its methyl ester, are relatively stable to treatment with alkali. It appears, therefore, that when the $C_{(15}$ atom of the picrotoxinin skeleton is present in a lactone ring and the oxygen function at $C_{(6)}$ in a hydroxyl group, the compounds concerned are alkali-sensitive whereas derivatives in which either of these conditions is not fulfilled are stable. Conroy [6] has postulated that the degradation of dihydropicrotoxinin (XVI) with sodium carbonate proceeds by two successive retro-aldol condensations at (a) and (b) according to the annexed scheme. On the basis of this mechanism it is obvious that the presence of a free 6-hydroxyl group in the picrotoxinin skeleton is necessary for fission of the 5 : 6-bond, and therefore β-bromopicrotoxininic acid (X), in which this oxygen function is present in an ether link, would not be expected to be degraded by alkali. Further, picrotoxic acid, picrotoxinindicarboxylic acid, and their methyl esters, which respectively contain β-hydroxy-acid and β-hydroxy-ester systems, might not be expected to undergo retro-aldol condensation with fission of the 5 : 6-bond since it has been shown [12] that β-hydroxy-acids and their ethyl esters undergo this scission only when there is at least one phenyl residue in the α-position or two in the β-position and even then the use of hot 15—20% aqueous potassium hydroxide seems to be necessary. The stability of picrotoxic acid and its derivatives to alkali thus appears to be in agreement with the structure (XII).

Further transformation products derived from the keto-alcohol (VIII; R = Me, R′ = ·CMe:CH_2, R′ = R″ = H) and its dihydro-derivative have been obtained and although the experimental evidence is, as yet, insufficient for the unequivocal formulation of these compounds, certain structural features have become apparent. Thus, on treatment with boiling water the keto-alcohol or its formate gave an anhydro-compound, $C_{15}H_{18}O_5$, which contains a molecule of water less than the parent alcohol. This anhydro-compound, which formed a dioxime and a yellow mono-2 : 4-dinitrophenylhydrazone, readily reduced Fehling's solution and ammoniacal silver nitrate on warming. On treatment with acetylating agents it was recovered unchanged and in agreement with this the



infrared absorption spectrum showed a total absence of absorption in the hydroxyl region. The ultraviolet spectrum of the compound included a band at 234 mμ (log ε 3·94) and it was readily shown that the *iso*propenyl double bond was not involved in the chromophoric system giving rise to this spectrum since the dihydro-keto-alcohol (VIII; R = Me, R′ = $CHMe_2$, R″ = R‴ = H) and its formate under similar conditions gave an analogous dihydro-anhydro-compound, $C_{15}H_{20}O_5$, the ultraviolet spectrum of which contained a band at 237 mμ (log ε 3·90). Similarly this product formed a dioxime and a yellow mono-2 : 4-dinitrophenylhydrazone. Methoxyl estimations on the compound, $C_{15}H_{18}O_5$, and its dihydro-derivative showed that both contained the methyl ester group known to be present in the parent keto-alcohol, the formate, and the respective dihydro-derivatives.

It is tentatively suggested that the compound, $C_{15}H_{18}O_5$, has the formula (XVII; R = ·CMe:CH_2) and arises from the keto-alcohol (VIII; R = Me, R′ = ·CMe:CH_2) by a reversed aldol condensation with subsequent dehydration as shown in the annexed scheme; the corresponding dihydro-compound, $C_{15}H_{20}O_5$ has the structure (XVII; R = $CHMe_2$). In the formation of the compounds $C_{15}H_{18}O_5$ and $C_{15}H_{20}O_5$ from the formate (VIII;

[12] Ivanov, *Ann. Univ. Sofia, II, Faculté phys.-math., Livre* 2, 1938—1939, **35**, 337; *Chem. Abs.*, 1940, **34**, 2348.

R = Me, R′ = ·CMe:CH$_2$, R″ = R‴ = H) and its dihydro-derivative respectively it is assumed that the hydrolysis of the formyl group precedes the retro-aldol condensation envisaged in the above scheme. The presence in structures (XVII; R = ·CMe:CH$_2$) and (XVII; R = CHMe$_2$) respectively of a fully substituted *cyclo*pentenone ring is in agreement with the ultraviolet spectra [dihydrojasmone [13] (XVIII) shows a high-intensity absorption band at 237 mμ] and, although the infrared spectra of the compound, $C_{15}H_{18}O_5$, and its dihydro-derivative are very complex in the carbonyl region, they are not incompatible with the structures proposed. Thus, *e.g.*, the infrared spectrum (in mineral oil mull) of the dihydro-compound, $C_{15}H_{20}O_5$, showed bands at 1733, 1695 (with shoulders at 1706 and 1692), and 1639 cm.$^{-1}$. The absence of carbonyl bands at a higher frequency than 1733 cm.$^{-1}$ indicates that the *cyclo*pentanone structure originally present in the dihydro-keto-alcohol has been modified in the formation of the dihydro-anhydro-compound, $C_{15}H_{20}O_5$. It is probable that the yellow mono-2 : 4-dinitrophenylhydrazones are formed from the formyl group in the retro-aldol condensation products and that the insolubility of these derivatives in the reaction mixtures prevents interaction of the carbonyl group in the *cyclo*pentenone system with the reagent.

Experimental

Ultraviolet absorption spectra were measured in 95% alcohol with a Unicam spectrophotometer and infrared spectra in mineral oil mulls with either a Grubb-Parsons double-beam or a Perkin-Elmer model 21 instrument. The light petroleum used had b. p. 60—80°.

Methyl picrotoxate and dihydropicrotoxate were prepared from picrotoxinin and dihydropicrotoxinin respectively with potassium hydroxide in methanol according to Horrmann's procedure.[2] The infrared spectrum of methyl picrotoxate had bands at 3448 (OH), 1802 (γ-lactone), 1745 (ester), and 1650 cm.$^{-1}$ (double band of *iso*propenyl group).

With acetic anhydride–pyridine methyl picrotoxate gave a *monoacetate* which formed platelets, m. p. 156—157°, from ethyl acetate–light petroleum (Found: C, 59·0; H, 6·1; OMe, 8·7; Ac, 12·1. $C_{18}H_{22}O_8$ requires C, 59·0; H, 6·1; OMe, 8·5; Ac, 11·8%). Similarly formed, the *monoacetate* of methyl dihydropicrotoxate separated from ethyl acetate–light petroleum in needles, m. p. 170—171° (Found: C, 58·8; H, 6·5; Ac, 12·0. $C_{18}H_{24}O_8$ requires C, 58·7; H, 6·6; Ac, 11·7%).

Methyl Picrotoxolate (V; R = Me, R′ = ·CMe:CH$_2$, R″ = R‴ = H).—Potassium borohydride (3·5 g.), dissolved in water (15 ml.), was added to a solution of methyl picrotoxate (7 g.) in methanol (80 ml.) and water (80 ml.) at 45° and the mixture kept for 24 hr. at room temperature, added to 2N-hydrochloric acid (50 ml.), and concentrated in vacuum (to 100 ml.). The crystalline precipitate (6 g.) was collected 24 hr. later; further concentration of the mother-liquors gave more solid (2—3 g.) containing large amounts of boric acid and boron complexes. To remove boron compounds the combined crude product was dissolved in methanol (75 ml.), mixed with a solution of mannitol (30 g.) in 0·1N-sulphuric acid (100 ml.), heated under reflux for 2 hr., concentrated (to 100 ml.), and neutralised with sodium hydrogen carbonate. *Methyl picrotoxolate* was isolated by continuous extraction with ether (8 hr.) and crystallised from water and then from ethyl acetate–light petroleum, forming felted needles (3·0 g.), m. p. 166·5—170°, $[\alpha]_D^{21}$ +125° (*c* 1·06 in EtOH); the infrared spectrum had bands at 3413 (OH), 1736 (ester), and 1648 cm.$^{-1}$ (double bond of *iso*propenyl system) (Found: C, 56·3; H, 6·9. $C_{16}H_{22}O_7,H_2O$ requires C, 55·8; H, 7·0%). A sample of the ester was dried at 100°/1 mm. and the resulting hygroscopic powder analysed immediately (Found: C, 59·0; H, 6·8; OMe, 9·6. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; OMe, 9·5%). This compound, which was readily soluble in 2N-aqueous sodium hydroxide was precipitated on acidification with mineral acid, and did not react with ethereal diazomethane, with Fehling's solution, or with Tollens's reagent. Prepared with acetic anhydride and pyridine, the *diacetate* (V; R = Me, R′ = ·CMe:CH$_2$, R″ = R‴ = Ac) separated from ethyl acetate–light petroleum in rosettes of needles, m. p. 179—180° (Found: C, 58·8; H, 6·7; Ac, 22·9. $C_{20}H_{26}O_9$ requires C, 58·5; H, 6·4; Ac, 21·0%).

Methyl O-methylpicrotoxolate (V; R = R″ = Me, R′ = ·CMe:CH$_2$, R‴ = H) was prepared

[13] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Arnold, London, 1954, p. 96.

from methyl picrotoxolate with either methanolic hydrogen chloride or methyl sulphate–potassium carbonate in acetone, and formed needles, m. p. 155·5—157° (from ethyl acetate–light petroleum), not immediately soluble in 2N-aqueous sodium hydroxide (Found: C, 59·8; H, 7·2; OMe, 18·2. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1; OMe, 18·2%). Prepared with acetic anhydride–pyridine, the *acetate* (V; R = R″ = Me, R′ = ·CMe:CH$_2$, R‴ = Ac) separated from ethyl acetate–light petroleum in needles, m. p. 144—146° (Found: C, 59·7; H, 6·9; OMe, 18·5; Ac, 13·5. $C_{19}H_{26}O_8$ requires C, 59·7; H, 6·9; OMe, 16·2; Ac, 11·2%). Hydrolysis of methyl *O*-methylpicrotoxolate with 0·5N-sodium hydroxide and isolation by continuous extraction with ether gave *O-methylpicrotoxolic acid* (V; R = R‴ = H, R′ = ·CMe:CH$_2$, R″ = Me) which separated from benzene–ethyl acetate in needles, m. p. 221—222·5° (Found: C, 58·9; H, 6·7; OMe, 9·9. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; OMe, 9·5%). With ethereal diazomethane this acid regenerated methyl *O*-methylpicrotoxolate, m. p. and mixed m. p. 155—157°.

Oxidation of Methyl Picrotoxolate to Methyl Picrotoxate.—Methyl picrotoxolate (0·5 g.), dissolved in water (12 ml.), was added to sodium dichromate (1·5 g.) in water (8 ml.) and concentrated sulphuric acid (1 ml.) at room temperature. Colourless needles (80 mg.) of methyl picrotoxate which separated were collected 23 hr. later; more material (310 mg.) was isolated from the mother-liquors with ether. On purification from benzene this ester formed needles, m. p. and mixed m. p. 168·5—170°, having the requisite infrared absorption spectrum.

Methyl Dihydropicrotoxolate (V; R = Me, R′ = CHMe$_2$, R″ = R‴ = H).—Reduction of methyl dihydropicrotoxate (4 g.) with potassium borohydride (3 g.) under the conditions used for the preparation of methyl picrotoxolate gave *methyl dihydropicrotoxolate* which separated from ethyl acetate in needles (1·9 g.), m. p. 157—161° (Found, on a sample dried at 80°/0·3 mm.: C, 58·2; H, 7·4; OMe, 9·3. $C_{16}H_{24}O_7$ requires C, 58·5; H, 7·4; OMe, 9·4%). The same compound was formed by the hydrogenation of methyl picrotoxolate in ethyl acetate with a platinum catalyst and had m. p. and mixed m. p. 157—161° and the requisite infrared absorption spectrum. This ester gave a *diacetate* (V; R = Me, R′ = CHMe$_2$, R″ = R‴ = Ac), forming needles, m. p. 180—181°, from ethyl acetate–light petroleum (Found: C, 58·1; H, 7·1; Ac, 18·1. $C_{20}H_{28}O_9$ requires C, 58·2; H, 6·8; Ac, 20·9%). On oxidation in water (4 ml.) with sodium dichromate (0·5 g.) in 10% sulphuric acid (3 ml.) methyl dihydropicrotoxolate (0·17 g.) gave methyl dihydropicrotoxate (0·09 g.) which separated from benzene in needles, m. p. and mixed m. p. 209—210°.

Oxidation of Methyl Picrotoxolate with Sodium Metaperiodate.—A solution of methyl picrotoxolate (1·5 g.) in water (40 ml.) was treated with sodium metaperiodate (3·5 g.) in water (18 ml.) at room temperature and the crystalline precipitate of the *keto-formate* (VIII; R = ·CMe:CH$_2$, R′ = CHO), which started to separate almost immediately, was collected 1 hr. later and crystallised from ethyl acetate, forming prisms (1·3 g.), m. p. 185—202° (decomp.), $[\alpha]_D^{23}$ +125° (*c* 0·80 in $CHCl_3$) $\lambda_{max.}$ 306 mμ (log ε 1·75) (Found: C, 59·6; H, 6·1; OMe, 9·5. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; OMe, 9·6%). The infrared absorption spectrum of this compound had bands at 3436 (OH), 1776 (C:O in five-membered ring), 1730 (Me ester), 1709 (formate ester) and 1653 cm.$^{-1}$ (double bond of *iso*propenyl group). Treatment of the keto-formate (0·5 g.) with concentrated sulphuric acid (3 ml.) in water (100 ml.) at room temperature for 10 days gave the *keto-alcohol* (VIII; R = ·CMe:CH$_2$, R′ = H) which was isolated by continuous extraction with ether and crystallised from ethyl acetate, forming stout needles (0·35 g.), m. p. 167—172°, $[\alpha]_D^{25}$ +137° (*c* 0·90 in EtOH), $\lambda_{max.}$ 304 mμ (log ε 1·5) (Found: C, 60·3; H, 7·0; OMe, 10·5. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8; OMe, 10·5%). This alcohol showed infrared bands at 3448, 3390 (OH), 1770 (C:O in five-membered ring), 1701 [Me ester; this band is shifted from the more usual frequency at *ca.* 1735 cm.$^{-1}$ and although the reason for this shift is not apparent, the corresponding dihydro-compound (VIII; R = CHMe$_2$, R′ = H) shows the normal ester frequency (see below)], and 1645 cm.$^{-1}$ (double bond of *iso*propenyl system). On treatment with acetic anhydride, 95% formic acid, and pyridine this alcohol gave the keto-formate (VIII; R = ·CMe:CH$_2$, R′ = CHO), m. p. and mixed m. p. 185—202° (decomp.), with the requisite infrared absorption spectrum. It formed a *monoacetate* (VIII; R = ·CMe:CH$_2$, R′ = Ac) which separated from ethyl acetate–light petroleum in stout needles, m. p. 135—136° (Found: C, 60·7; H, 6·7; Ac, 12·7. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6; Ac, 12·7%), and a 2 : 4-*dinitrophenylhydrazone* in yellow needles, m. p. 228—233° (decomp.), from alcohol (Found: C, 52·9; H, 5·1; N, 11·7; OMe, 7·0. $C_{21}H_{24}O_9N_4$ requires C, 52·9; H, 5·1; N, 11·8; OMe, 6·5%). With a boiling solution of 2 : 4-dinitrophenylhydrazine (150 mg.)

in alcohol (10 ml.) and concentrated hydrochloric acid (0·1 ml.) the keto-formate (VIII; R = ·CMe:CH_2, R′ = CHO) (50 mg.) gave the same 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 228—233°. The keto-alcohol was recovered quantitatively after treatment with sodium metaperiodate, periodic acid, lead tetra-acetate, or boiling toluene for 2 hr.

Oxidation of Methyl Dihydropicrotoxolate with Sodium Metaperiodate.—Under the conditions employed for methyl picrotoxolate the oxidation of methyl dihydropicrotoxolate (1 g.) with sodium metaperiodate (1·5 g.) gave the *dihydro-keto-formate* (VIII; R = $CHMe_2$, R′ = CHO) which separated from ethyl acetate in hard prisms (0·65 g.), m. p. 208—211° (decomp.), $\lambda_{max.}$ 307 mμ (log ε 1·4), having infrared absorption bands at 3413 (OH), 1776 (C:O in five-membered ring), 1730 (Me ester) and 1706 cm.$^{-1}$ (formate ester) (Found: C, 58·8; H, 6·8. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8%). Hydrolysis of this product (0·5 g.) with sulphuric acid (3 ml.) in water (100 ml.) at room temperature for 10 days gave the *dihydro-keto-alcohol* (VIII; R = $CHMe_2$, R′ = H) which was isolated with ether and crystallised from ethyl acetate, forming stout needles, m. p. 200—204°, $[\alpha]_D^{26}$ +114° (*c* 1·23 in EtOH), $\lambda_{max.}$ 304 mμ (log ε 1·5), infrared absorption bands at 3472, 3436 (OH), 1761 (C:O in five-membered ring) and 1736 cm.$^{-1}$ (Me ester) (Found: C, 60·2; H, 7·2; OMe, 10·3. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4; OMe, 10·4%). This product was recovered quantitatively after treatment with sodium metaperiodate, periodic acid, lead tetra-acetate, or boiling toluene for 2 hr. It regenerated the dihydro-keto-formate, m. p. and mixed m. p. 208—211°, and formed an *acetate* (VIII; R = $CHMe_2$, R′ = Ac), which separated from ethyl acetate in prisms, m. p. 184—187° (Found: C, 59·9; H, 7·2; Ac, 12·4. $C_{17}H_{24}O_7$ requires C, 60·0; H, 7·1; Ac, 12·6%), and a 2 : 4-*dinitrophenylhydrazone*, in yellow needles, m. p. 233—234° (decomp.) from methanol (Found: C, 52·3; H, 5·4; N, 11·5. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·5; N, 11·7%).

Anhydro-compound (XVII; R = ·CMe:CH_2).—Treatment of the keto-alcohol (VIII; R = ·CMe:CH_2, R′ = H) (100 g.) with boiling water (25 ml.) for 40 min. gave the *anhydro-compound* (80 mg.), m. p. 148—150° which separated from methanol in long needles, m. p. 150—152°, $\lambda_{max.}$ 234 mμ (log ε 3·94), infrared absorption bands at 1736, 1701 (with shoulders at 1706 and 1695), and 1653 cm.$^{-1}$ (Found: C, 64·8; H, 6·6; OMe, 11·3. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5; OMe, 11·2%). The same compound, m. p. and mixed m. p. 150—152° and identical infrared spectrum, was obtained by boiling the keto-formate (VIII; R = ·CMe:CH_2, R′ = CHO) with water for 3½ hr. It did not react with acetic anhydride and pyridine or lead tetra-acetate, rapidly reduced Fehling's solution and ammoniacal silver nitrate on warming, decolorised cold bromine water, and with 2N-aqueous sodium hydroxide at room temperature gave an intractable gum. The 2 : 4-*dinitrophenylhydrazone* formed yellow needles, m. p. 240—251° (decomp.) (from chloroform–ethanol), $\lambda_{max.}$ 252, 362 mμ (log ε 4·12, 4·46) (Found: C, 55·3; H, 4·9; N, 12·0. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%), and the *dioxime*, needles, m. p. 214—216° (decomp.), from alcohol (Found: C, 58·0; H, 6·3; N, 8·9. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%).

Dihydro-anhydro-compound (XVII; R = $CHMe_2$).—On being boiled with water (25 ml.) for 40 min. the dihydro-keto-alcohol (VIII; R = $CHMe_2$, R′ = H) (100 mg.) gave the *dihydro-anhydro-compound* (80 mg.), forming needles, m. p. 161—162° (from light petroleum), $\lambda_{max.}$ 237 mμ (log ε 3·90), infrared absorption bands at 1733, 1695 (with shoulders at 1706 and 1692), and 1639 cm.$^{-1}$ (Found: C, 64·2; H, 7·2; OMe, 11·2. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2; OMe, 11·1%). The same compound (0·45 g.), m. p. and mixed m. p. 161—162°, with the same infrared absorption spectrum, was formed by boiling the dihydro-keto-formate (VIII; R = $CHMe_2$, R′ = CHO) (0·7 g.) with water for 2 hr. The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–alcohol in yellow needles, m. p. 221—223° (decomp.) (Found: C, 54·9; H, 5·1; N, 12·1. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·3; N, 12·2%), and the *dioxime* from alcohol in needles, m. p. 204—206° (decomp.) (Found: C, 57·5; H, 7·3; N, 8·7. $C_{15}H_{22}O_5N_2$ requires C, 58·0; H, 7·2; N, 9·0%).

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates in this Department.

UNIVERSITY OF LIVERPOOL. [*Received, July 11th*, 1957.]

990. *The Structure of Picrotoxic Acid.*

By D. E. Hathway.

The chemical relations between picrotoxic acid and picrotoxinin derivatives establish the functional groups, which are confirmed by infrared measurement. Methylation of methyl dihydro-*O*-methylpicrotoxate by a modified Purdie procedure, hydrolysis of methyl dihydrodi-*O*-methylpicrotoxate by hydrazine, and preparation of a picrotoxinin monoacetate are described. The present work in conjunction with Conroy's carbon skeleton [1] for the parent compound suggests two structures for picrotoxic acid, of which (I) is preferred.

In 1948, an investigation of the chemistry of picrotoxic acid and picrotoxinin was begun because, although the structure of several degradation products had been established,[2] these were obtained by reactions sufficiently drastic to obscure the structural relation to the parent compound.

Mercer and Robertson [2] had prepared a methylation product of dihydropicrotoxic acid to which the partial formula $Pr^{i}\cdot C_{11}H_{10}O_3(OMe)_2\cdot CO_2Me$ was given, but the reaction conditions were unsuited for preparative work. Further work on this and many related compounds has now established this partial formula for methyl dihydrodi-*O*-methylpicrotoxate. Methylation of dihydropicrotoxic acid by methyl sulphate and potassium carbonate or by diazomethane gave this ester which underwent further methylation by the Purdie method faster than the original acid or ester, and very rapidly by a modified Purdie reaction in *NN*-dimethylformamide. Picrotoxic acid was similarly converted into methyl dihydrodi-*O*-methylpicrotoxate by way of methyl *O*-methylpicrotoxate (identical with Sutter and Schlittler's " substance C " [3]) and methyl di-*O*-methylpicrotoxate. Dihydropicrotoxic acid was recovered on demethylation of methyl dihydro-*O*-methylpicrotoxate and the related dimethyl ether by acid. Hydrolysis of methyl dihydropicrotoxate or its methyl ether by alkali gave the corresponding acids. Methyl dihydrodi-*O*-methyl picrotoxate was resistant to alkali; but treatment with hydrazine hydrate in boiling 2-ethoxyethanol gave the acid, and methylamine was liberated ($R\cdot CO_2Me + N_2H_4,H_2O \longrightarrow R\cdot CO_2H + NH_2\cdot OH + NH_2Me$). Methylation of dihydro-*O*-methylpicrotoxic and dihydrodi-*O*-methylpicrotoxic acid with diazomethane regenerated the esters. Infrared evidence confirms the assignment of functional groups involved in the reactions between these compounds. Thus methyl dihydrodi-*O*-methylpicrotoxate shows no bands due to hydroxyl, but bands at 1100—1120 cm.$^{-1}$ due to ether linkages, at 1734 cm.$^{-1}$ due to an ester-carboxyl group, and at 1785 cm.$^{-1}$ due to an unreactive γ-lactone group.

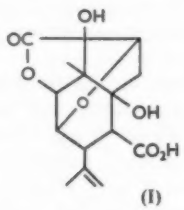
Dihydropicrotoxic acid is stable to dichromate in dilute sulphuric acid at 100°, fuming nitric at 100°, boiling 2N-potassium permanganate, Oppenauer reagents, red phosphorus and boiling hydriodic acid, and glycol-splitting reagents. The hydroxyl groups of picrotoxic and dihydropicrotoxic acid are therefore tertiary and not attached to adjacent carbon atoms, and suppression of the double bond by hydrogenation arrests aromatisation. One of the hydroxyl groups of these acids is acidic, as it is methylated by diazomethane and the esters are soluble in alkali. That the acidity [4] of methyl picrotoxate is due to the hydroxyl group rather than to lactone fission is shown by the alkali-insolubility of methyl *O*-methylpicrotoxate. This acidic hydroxyl group therefore belongs to an α-hydroxycarboxylic group, and in this connection the similar acidic properties of methyl quinate

[1] Conroy, *J. Amer. Chem. Soc.*, 1952, **74**, 491.
[2] Mercer, Robertson, and Cahn, *J.*, 1935, 997; Mercer and Robertson, *J.*, 1936, 288; Harland and Robertson, *J.*, 1939, 935; Sutter and Schlittler, *Helv. Chim. Acta*, 1947, **30**, 403, 2102.
[3] Sutter and Schlittler, *Helv. Chim. Acta*, 1950, **33**, 902.
[4] Horrmann, *Annalen*, 1916, **411**, 273.

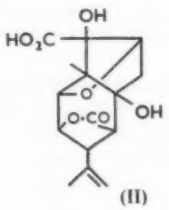
may be cited. Since this carboxyl group belongs either to the free carboxylic acid group or to the γ-lactone group, two formulæ are possible for picrotoxic acid (I, II) on the assumption of Conroy's carbon skeleton for picrotoxinin.[1] I am much indebted to a Referee for pointing out that the dihydro-derivative of an acid (II) should be cleaved by oxidising agents such as nitric acid in the sense (III)—(IV), and that absence of such fission and of reaction with lead tetra-acetate, points to formula (I) for picrotoxic acid. I agree with this view.

O-Dihydrodimethylnorpicrotoxamine and the corresponding amine from dihydropicrotoxic acid were isolated in yields unpromising for further degradation.

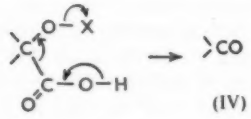
The bands at 3610 and 3500 cm.$^{-1}$ in the spectrum of picrotoxinin are due to a hydroxyl group, previously suspected[4] from Zerewitinoff estimation. This hydroxyl group is tertiary as picrotoxinin cannot be oxidised to a ketone or acetylated by the usual pro-



(I)



(II)



(III) (IV)

cedure. Picrotoxinin has now been acetylated by boiling acetic anhydride and sodium acetate: the monoacetate obtained could not be prepared from Horrmann's anhydropicrotin.[5] Picrotoxinin acetate gave picrotoxic acid on acid hydrolysis, α-dihydropicrotoxinin acetate on hydrogenation, methyl *O*-methylpicrotoxate on treatment with diazomethane and potassium hydroxide, and a **6 : 1** mixture of α- and β-picrotoxinone acetate on oxidation by chromic oxide or ozonolysis. Ozonolysis therefore gave an equilibrium mixture of keto–enol isomers, for the α-isomer changed into the β-isomer when heated, both isomers gave a single crystalline **2 : 4**-dinitrophenylhydrazone, and the α-isomer was not reducible catalytically. The acetylation product of picrotoxinin is therefore a normal array of functional groups, $C_{11}H_{10}O_3(\cdot CO\cdot O\cdot)(OAc)(CMe{:}CH_2)$. In contrast to the other picrotoxinin derivatives, it has the convulsant properties of the parent compound, and this can be interpreted as biological evidence of similar chemical structure. Its infrared spectrum is similar to that of the parent compound—bands at **1645** and **896** cm.$^{-1}$ due to the *iso*propenyl group, and at **1125** cm.$^{-1}$ due to an ether linkage. Picrotoxinin shows intense split peaks at **1780** and **1765** cm.$^{-1}$, and the acetate an intense band at **1785** cm.$^{-1}$, all due to two γ-lactone groups. In the latter compound, the split peak is lost on account of the presence at **1730** cm.$^{-1}$ of a band due to an acetate group, a view which is confirmed by the presence of a further band at **1235** cm.$^{-1}$. The hydroxyl band of picrotoxinin has previously been mentioned. The presence of two γ-lactone groups in these compounds can only be deduced from the intensity of the split peaks, and in this respect the earlier deductions by Conroy[1] and by Benstead *et al.*[6] require modification. Santonin has now been used for comparison. Intense split peaks at **1795** and **1772** cm.$^{-1}$ for α-dihydropicrotoxinin, and at **1805** and **1774** cm.$^{-1}$ for picrotin agree with the presence of two γ-lactone groups.

Treatment of picrotoxinin with hydroxylamine did not effect lactone fission,[7] and in order to achieve a stepwise degradation procedure reduction of picrotoxinin and picrotin

[5] Horrmann, *Ber.*, 1910, **43**, 1903.
[6] Benstead, Brewerton, Fletcher, Martin-Smith, Slater, and Wilson, *J.*, 1952, 1042.
[7] Clemo and Cocker, *J.*, 1946, 30.

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by lithium aluminium hydride and treatment of the resulting polyhydric alcohols with glycol-splitting reagents was initiated.[8]

Experimental

Methyl Dihydro-O-methylpicrotoxate.—(*a*) An acetone solution (200 ml.) of anhydrous dihydropicrotoxic acid [2] (5 g.) was refluxed with methyl sulphate (4 ml.) and potassium carbonate (10 g.) for 5 hr. Crude *methyl dihydro-O-methylpicrotoxate*, recovered in the usual way, crystallised from water in stout needles (4·6 g.), m. p. 165°, $[\alpha]_D^{20}$ +94° (*c* 1·0 in EtOH) [Found: C, 60·0; H, 7·1; OMe, 18·2. $C_{15}H_{18}O_5(OMe)_2$ requires C, 60·0; H, 7·10; OMe, 18·2%], insoluble in aqueous alkali.

(*b*) A suspension of anhydrous dihydropicrotoxic acid (1 g.) in absolute methanol (20 ml.) was treated with excess of diazomethane. The product (0·9 g.) crystallised from water, forming needles, m. p. 165°, alone or mixed with methyl dihydro-*O*-methylpicrotoxate.

Methyl Dihydrodi-O-methylpicrotoxate.—(*a*) A methyl iodide solution (25 ml.) of methyl dihydro-*O*-methylpicrotoxate (2 g.) was refluxed for 2 days with freshly prepared silver oxide [9] (4 g.) and anhydrous sodium sulphate (1 g.), 4 further additions of silver oxide (1 g. each) being made at 10 hr. intervals. Methyl dihydrodi-*O*-methylpicrotoxate (2·03 g.) crystallised from light petroleum (b. p. 80—100°) in stout needles, m. p. and mixed m. p. 146—147°, $[\alpha]_D^{20}$ +112° (*c* 1·0 in EtOH) [Found: C, 60·9; H, 7·4; OMe, 26·1. Calc. for $C_{15}H_{17}O_4(OMe)_3$: C, 61·05; H, 7·3; OMe, 26·2%].

(*b*) Methyl dihydro-*O*-methylpicrotoxate (10 g.) in *NN*-dimethylformamide (5 ml.) was refluxed with methyl iodide (10 ml.), silver oxide (10 g.), and anhydrous sodium sulphate (1 g.) for 3 hr. Methyl dihydrodi-*O*-methylpicrotoxate was precipitated from dimethylformamide solution by water, and crystallised from light petroleum, forming needles, m. p. 146—147°. This ester is vesicant and is stable to boiling aqueous 50% potassium hydroxide.

Methyl O-Methylpicrotoxate.—(*a*) An acetone solution (100 ml.) of methyl picrotoxate [4] (3·25 g.) was similarly refluxed with methyl sulphate (2·2 ml.) and potassium carbonate (5 g.) for 5 hr. Methyl *O*-methylpicrotoxate crystallised from water in prisms (2·6 g.), m. p. 177° (depressed to *ca.* 150° by admixture with methyl picrotoxate, m. p. 172°, and undepressed by admixture with Sutter and Schlittler's [3] " substance C "), $[\alpha]_D^{20}$ +105° (*c* 2·2 in EtOH) (Found: C, 60·6; H, 6·4; OMe, 17·4. Calc. for $C_{17}H_{22}O_7$: C, 60·4; H, 6·5; OMe, 18·3%). Unlike methyl picrotoxate,[4] methyl *O*-methylpicrotoxate was insoluble in aqueous alkali.

(*b*) Methyl picrotoxate (1 g.) in methanol (10 ml.) was methylated by excess of diazomethane, and methyl *O*-methylpicrotoxate (1 g.) was obtained in prisms, m. p. 177°, undepressed by Sutter and Schlittler's [3] " substance C ".

Methyl Di-O-methylpicrotoxate.—Methyl *O*-methylpicrotoxate (2·4 g.) in *NN*-dimethylformamide (4 ml.) was refluxed with methyl iodide (10 ml.), silver oxide (4 g.), and anhydrous sodium sulphate (1 g.) for 3 hr. Dilution of the dimethylformamide filtrate precipitated *methyl di-O-methylpicrotoxate* (2·3 g.) which crystallised from light petroleum (b. p. 100—120°) in lamellæ (2 g.), m. p. 124°, $[\alpha]_D^{20}$ +124° (*c* 2·1 in EtOH) (Found: C, 61·4; H, 6·8; OMe, 26·4. $C_{18}H_{24}O_7$ requires C, 61·4; H, 6·8; OMe, 26·4%). The same products were also obtained from picrotoxic acid.[4]

Hydrogenation of Methyl Di-O-methylpicrotoxate.—An ethanolic solution of this ester (1·75 g.) was hydrogenated at 1 atm., in the presence of Adams platinic oxide catalyst and one drop of 12N-hydrochloric acid. Methyl dihydrodi-*O*-methylpicrotoxate (1·7 g.) crystallised from light petroleum (b. p. 80—100°) in needles, m. p. and mixed m. p. 146—147°.

Demethylation of Methyl Dihydro-O-methylpicrotoxate.—Methyl dihydro-*O*-methylpicrotoxate (3 g.) was refluxed with 90% orthophosphoric acid (40 ml.) for 1 hr., then the mixture was diluted and extracted with ether for 1 day. Evaporation left the crude product which was dissolved in 2N-sodium hydrogen carbonate, and the whole then extracted with ether for 1 day. Acidification of the aqueous phase with hydrochloric acid gave dihydropicrotoxic acid (2·6 g.), m. p. 260°, isolated by extraction and crystallisation from ethyl acetate.

Demethylation of Methyl Dihydrodi-O-methylpicrotoxate.—Methyl dihydrodi-*O*-methylpicrotoxate (2 g.) was refluxed with freshly distilled hydriodic acid (25 ml., *d* 1·7) and 90%

[8] Holker, Holker, McGookin, Robertson, Sergeant, and Hathway, *J.*, 1957, 3746.
[9] Helferich and Klein, *Annalen*, 1926, **450**, 219.

orthophosphoric acid (10 ml.) for 4 hr., then the mixture was diluted and worked up as in the preceding experiment. Dihydropicrotoxic acid (1·8 g.) crystallised from ethyl acetate, forming needles, m. p. and mixed m. p. 260°.

*Hydrolysis of Methyl Dihydro-*O*-methylpicrotoxate.*—Methyl dihydro-*O*-methylpicrotoxate (2 g.) was refluxed with 2N-potassium hydroxide (25 ml.) for 2 hr. Acidification yielded felted needles of *dihydro-*O*-methylpicrotoxic acid* which crystallised from water in parallelepipeds, m. p. 240°, $[\alpha]_D^{20}$ +86° (*c* 1·1 in EtOH) (Found: C, 58·85; H, 6·5. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·75%). Treatment of a solution of the acid (500 mg.) in ether with excess of diazomethane regenerated the ester (500 mg.), m. p. and mixed m. p. 165°.

*Hydrolysis of Methyl Dihydrodi-*O*-methylpicrotoxate.*—A 2-ethoxyethanol solution (27 ml.) of methyl dihydro-*O*-dimethylpicrotoxate (5 g.) was refluxed with 60% hydrazine hydrate (50 ml.) for 30 hr., nitrogen being passed successively through the mixture and 0·1N-hydrochloric acid (15 ml.). The reaction mixture was diluted, acidified with 12N-hydrochloric acid, then kept at 0°. Dihydrodi-*O*-methylpicrotoxic acid was recovered and crystallised from water in needles (4·95 g.), m. p. 206—207°, $[\alpha]_D^{20}$ +109° (*c* 1·1 in EtOH) [Found: OMe, 18·2. Calc. for $C_{15}H_{18}O_5(OMe)_2$: OMe, 17·9%]. Concentrated aqueous hexachloroplatinic acid (5 ml.) was added to the contents of the gas absorption vessel which was then kept at 0°. Methylamine chloroplatinate (3 g.) was recovered and dried at 100°/15 mm. [Found: C, 5·0; H, 2·0; N, 6·0. $(CH_5N)_2PtCl_6$ requires C 5·1; H 2·1; N, 6·0%]. Treatment of an ether solution of dihydrodi-*O*-methylpicrotoxic acid (500 mg.) with excess of diazomethane regenerated methyl dihydrodi-*O*-methylpicrotoxate (500 mg.), m. p. and mixed m. p. 146—147°.

Attempted Oxidations of Dihydropicrotoxic Acid.—This acid was recovered unchanged from treatment with: (1) N-sodium dichromate in 2N-sulphuric acid at 100° for 8 hr., (2) nitric acid (*d* 1·45) at 100° for 5 hr., (3) excess of boiling 2N-potassium permanganate for 6 hr., (4) excess of *cyclo*hexanone and aluminium *tert.*-butoxide in boiling absolute dioxan for 6 hr., (5) red phosphorus and excess of boiling hydriodic acid (*d* 1·7) for 6 hr., (6) excess of lead tetra-acetate in warm acetic acid, and (7) excess of periodic acid in aqueous ethanol.

*Schmidt Reaction with Dihydrodi-*O*-methylpicrotoxic Acid.*—To a stirred mixture of a sulphuric acid solution (15 ml.; *d* 1·84) of dihydrodi-*O*-methylpicrotoxic acid (2·3 g.) and chloroform (35 ml.) at 50°, sodium azide (520 mg.) was added portionwise throughout 1 hr., and the mixture was stirred for a further 1 hr. at 50°, then kept at 20° for 1 day, and diluted with ice. The aqueous phase was neutralised with sodium hydrogen carbonate and extracted with ether for 2 days. Evaporation of the solvent left an oily amine (0·5 ml.) which did not liberate ammonia on treatment with boiling alkali. With acetic anhydride–pyridine the product gave N-*acetyldihydrodi-*O*-methylnorpicrotoxamide* which formed rhombs, m. p. 285°, from dilute acetic acid [Found: C, 61·0; H, 7·55; N, 4·1. $C_{14}H_{17}O_3(OMe)_2{\cdot}NHAc$ requires C, 61·2; H, 7·65; N, 4·0%].

*Dihydrodi-*O*-methylpicrotoxamide* crystallised from dilute acetic acid in felted needles, m. p. 262° [Found: C, 60·3; H, 7·5; N, 4·2. $C_{14}H_{17}O_3(OMe)_2{\cdot}CO{\cdot}NH_2$ requires C, 60·2; H, 7·4; N, 4·15%], and was converted under the conditions of the Hofmann reaction into the same amine, characterised as *N*-acetyl derivative, m. p. 285°.

Schmidt Reaction with Dihydropicrotoxic Acid.—When a stirred mixture of a sulphuric acid solution (40 ml.; *d* 1·84) of dihydropicrotoxic acid (6·25 g.) and chloroform (80 ml.) at 50° was treated with sodium azide (1·82 g.) as above, extraction of the neutralised aqueous phase yielded a small quantity of amine which on treatment with acetic anhydride–pyridine gave a *triacetate*, needles (from dilute acetic acid) (3 mg.), m. p. 287° (Found: C, 59·2; H, 6·5. $C_{20}H_{27}O_8N$ requires C, 59·0; H, 6·6%) (test for N positive).

Picrotoxinin Acetate.—When picrotoxinin (5 g.) was refluxed with acetic anhydride (15 ml.) and fused sodium acetate (300 mg.) for 16 hr., crude product recovered in the usual way crystallised from acetic acid (charcoal) in stout pyramids (3 g.), m. p. 255°, $[\alpha]_D^{20}$ +18° (*c* 1·7 in C_5H_5N), of *picrotoxinin acetate* (Found: C, 61·1; H, 5·5; Ac, 15·7. $C_{17}H_{18}O_7$ requires C, 61·1; H, 5·4; Ac, 13·0%). Horrmann's anhydropicrotin,[5] m. p. 315° (decomp.) (Found: C, 61·4; H, 5·5. Calc. for $C_{15}H_{16}O_6$: C, 61·6; H, 5·5%), remained unchanged by this treatment.

Hydrogenation of Picrotoxinin Acetate.—Hydrogenation of an acetic acid solution (100 ml.) of picrotoxinin acetate (750 mg.) at 1 atm., in the presence of Adams platinic oxide and 1 drop of 12N-hydrochloric acid gave *α-dihydropicrotoxinin acetate* (700 mg.) which crystallised from acetic acid in hexahedra, m. p. 250° (undepressed by admixture with a specimen prepared by direct acetylation of α-dihydropicrotoxinin), $[\alpha]_D^{20}$ +14° (*c* 1·8 in C_5H_5N) (Found: C, 60·5; H, 6·25. $C_{17}H_{20}O_7$ requires C, 60·7; H, 5·9%).

XUM

Acid-hydrolysis of Picrotoxinin Acetate.—Picrotoxinin acetate (350 mg.) was refluxed with N-sulphuric acid (20 ml.) for 1 day, then a small volume of distillate was collected and shown to contain acetic acid by the isolation of 2-methylbenziminazole picrate, m. p. and mixed m. p. 214°. Picrotoxic acid (300 mg.) was recovered as needles, m. p. and mixed m. p. 230°.

Reaction of Picrotoxinin Acetate with Diazomethane.—A methanolic solution (20 ml.) of picrotoxinin acetate (1 g.) was treated with excess of diazomethane and an aqueous solution (0·5 ml.) of potassium hydroxide (50 mg.) for 2 days. Methyl *O*-methylpicrotoxate, isolated in the usual way, crystallised from water in needles (900 mg.), m. p. 176°, identical with Sutter and Schlittler's " substance C."[3]

Ozonolysis of Picrotoxinin Acetate.—Ozonised oxygen was conducted through an ethyl acetate solution (700 ml.) of picrotoxinin acetate (4 g.) at 0° for 5 hr. The ozonide gradually separated in prisms; it was decomposed with ice-water; the crude product (3·8 g.) melted at 189°. A hot ethanolic solution (300 ml.) of the product deposited rhombs (3 g.), m. p. 212—214°, of *α-picrotoxinone acetate*, $[\alpha]_D^{20}$ +89° (*c* 0·6 in C_5H_5N) (Found: C, 57·1; H, 4·9. $C_{18}H_{16}O_6$ requires C, 57·1; H, 4·8%). Partial evaporation of the mother-liquors gave crystals which recrystallised from acetic acid in cubes (0·5 g.), m. p. 276° (decomp.), of *β-picrotoxinone acetate*, $[\alpha]_D^{20}$ +80° (*c* 0·2 in C_5H_5N) (Found: C, 57·0; H, 4·7%), identical with the product obtained from the α-isomer at 220°/0·01 mm. Treatment of an aqueous solution of α- or β-picrotoxinone acetate (100 mg.) with 2 : 4-dinitrophenylhydrazone sulphate reagent in 10N-sulphuric acid gave a precipitate of 2 : 4-*dinitrophenylhydrazone* which crystallised from chloroform–alcohol in orange cubes, m. p. 256° (decomp.) (Found: C, 51·1; H, 3·7; N, 11·0. $C_{22}H_{20}O_{11}N_4$ requires C, 51·2; H, 3·9; N, 10·9%). In a parallel experiment, the distillate from the decomposition of the ozonide was used for the estimation and identification of formaldehyde (0·5 mol.) as the dimedone derivative, m. p. 189—191°. An acetic acid solution of α-picrotoxinone acetate was recovered unchanged after attempted hydrogenation at 1 atm. in the presence of Adams platinic oxide.

Oxidation of picrotoxinin acetate with chromium trioxide in acetic acid similarly afforded a mixture (6 : 1) of α- and β-picrotoxinone acetate.

Attempted Reaction of Picrotoxinin with Hydroxylamine.—Picrotoxinin was recovered unchanged from treatment of a boiling ethanolic solution (1 g. in 6 ml.) with hydroxylamine hydrochloride (1 g.) and fused sodium acetate (2 g.) for 5 hr.

Silver Oxide Oxidation of Picrotoxinin.—An aqueous solution (200 ml.) of picrotoxinin (2·9 g.) was refluxed with silver oxide (4 g.) for 2 hr., then the filtrate was acidified with 12N-hydrochloric acid, silver halide removed, and the filtrate neutralised with sodium hydrogen carbonate. Extraction with ether and evaporation gave a residue of picrotoxinin which crystallised from water in needles (50 mg.), m. p. 204—205°. Extraction of the re-acidified aqueous phase with ether gave a residue (1 g.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in prisms, m. p. 290°, of αα-dimethylphthalide-3 : 4-dicarboxylic acid[10] (Found: C, 54·0; H, 4·7. Calc. for $C_{12}H_{10}O_6,H_2O$: C, 53·75; H, 4·5%).

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[10] Hansen, *Ber.*, 1933, **66**, 849.

991. *The Synthesis of Condensed Heterocyclic Systems. Part I. Use of 2-Vinylthiophen in the Diene Synthesis.*

By W. Davies and Q. N. Porter.

2-Vinylthiophen behaves as a moderately active diene with benzoquinone and maleic anhydride. The products give fair yields of 4 : 5-benzothionaphthen and, after dehydrogenation, thionaphthen-4 : 5-dicarboxylic anhydride respectively.

Recognition of the aromatic nature of thiophen has facilitated its substitution for benzene in many well-known condensations and synthetic processes; *e.g.*, reaction with phthalic anhydride [1] gives a tricyclic compound. On the other hand, relatively little synthetic use has been made of the differences, as opposed to the similarities, between thiophen and benzene derivatives: instances of such use are the formation [2] of bicyclic dianhydrides by action of maleic anhydride on the *S*-dioxides of dimethyl- and diphenylthiophen, and the reaction [3] of 3 : 4-dimethylthiophen 1 : 1-dioxide with thionaphthen 1 : 1-dioxide, the latter reacting in this case as a dienophile; other examples are the union [4] of maleic anhydride with 1 : 8 : 1′ : 8′-diacenaphthenothiophen, and with 2-vinylthiophen (I).[5]

The last-mentioned adduct was readily hydrolysed to 4 : 5 : 6 : 7-tetrahydrothionaphthen-4 : 5-dicarboxylic acid (II), the structure of which was proved by its conversion into thionaphthen on dehydrogenation and decarboxylation. The adduct—not previously analysed—has now been obtained in 49% yield and almost quantitatively converted into the dicarboxylic acid (II), m. p. 212°; Scully and Brown's acid was reported to be a mixture (m. p. not given) of *cis*- and *trans*-forms, m. p. 188—189° and 194—195°. The m. p. of some dicarboxylic acids varies according to the method of determination, and it is relevant that only one acid is obtained from the hydrolysis product of the analogous adduct of 3-vinylthionaphthen and maleic anhydride (following paper). Dehydrogenation, with sulphur, of the vinylthiophen adduct gave a 63% yield of thionaphthen-4 : 5-dicarboxylic anhydride. Incidentally, loss, from the acid (II), of the 5-carboxyl group only, either before or after aromatisation, could theoretically yield the still unknown [6] thionaphthen-4-carboxylic acid.

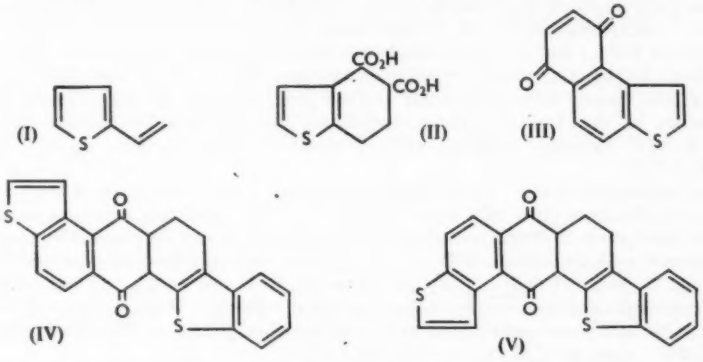
2-Vinylfuran is known to add to maleic anhydride, a tetrahydrocoumaronedicarboxylic anhydride being formed.[7] It is noteworthy that there the strong diene action of the furan ring itself towards maleic anhydride is not in evidence; as with the above more aromatic thiophen derivative the diene system which reacts is in part cyclic and in part exocyclic. Apart from the above two reactions with maleic anhydride, and the addition [8] of benzoquinone to 3-vinylthionaphthen, this use of vinyl heterocyclic compounds has apparently been hitherto neglected.

2-Vinylthiophen reacts slowly with benzoquinone, to give a 43% yield of 4 : 5-benzothionaphthen-1′ : 4′-quinone (III), and so far it has not proved possible to isolate an adduct which has not undergone dehydrogenation by excess of quinone. Lithium aluminium hydride reduces the quinone to 4 : 5-benzothionaphthen in high yield (this method of reduction of 1 : 4-naphthaquinone derivatives has been described for 9-thia-1 : 2-benzofluorene-1′ : 4′-quinone [8] and is of considerable value). Boyland and Manson [9] used

[1] Hartough and Meisel, "Compounds with Condensed Thiophen Rings," Interscience Pub. Inc., New York, 1954, p. 289.
[2] Melles, *Rec. Trav. chim.*, 1952, **71**, 869.
[3] Davies and Porter, following paper.
[4] Clapp, *J. Amer. Chem. Soc.*, 1939, **61**, 2733.
[5] Scully and Brown, *ibid.*, 1953, **75**, 6329.
[6] Badger, Crook, Davies, Farrer, and Kefford, *J.*, 1957, 2624.
[7] Paul, *Bull. Soc. chim. France*, 1943, **10**, 163.
[8] Davies, Porter, and Wilmshurst, *J.*, 1957, 3366.
[9] Boyland and Manson, *J.*, 1951, 1837.

lithium aluminium hydride to reduce 1 : 4-naphthaquinone, isolating 1 : 4-dihydroxytetralin and 4-hydroxy-1-tetralone. The former product was then converted into naphthalene by treatment with acid, while the latter gives 1-naphthol under similar conditions. In the present work the excess of lithium aluminium hydride is not only greater than that used by Boyland and Manson, but gradual addition of the quinone to all the lithium aluminium hydride ensures that a very large excess of the latter is present until near the end of the reaction. The analogous products intermediate between the quinone (III) and the thiahydrocarbon have not been isolated but may have been formed. This direct conversion of a quinone into an aromatic compound is often applicable (cf. Davies and Porter [3]).

The time required to produce from quinones a satisfactory yield of adduct shows that 2-vinylthiophen and 3-vinylthionaphthen are more reactive than their isosteres styrene and 1-vinylnaphthalene, probably owing to the lower aromaticity of the heterocyclic isosteres and the consequent greater double-bond character of their 2 : 3-bonds which causes the compounds to approximate more to true dienes. The well-known greater activity of vinylnaphthalenes than of styrene is also paralleled by the superiority of 3-vinyl-



thionaphthen over 2-vinylthiophen. For example, benzoquinone with 2-vinylthiophen gives a 43% yield of the product (III) in 8 hr., but an 80% yield of a similar product from 3-vinylthionaphthen [8] (yields calculated on the vinyl compounds). Moreover, during the preparation of the quinone (III) a bis-adduct from it and another molecule of 2-vinylthiophen is apparently not formed, whereas a 61% yield of the adduct (IV) or (V) is produced in 10 min. under the same conditions from the quinone (III) and 3-vinylthionaphthen. In making these rough comparisons the criterion has been a practical one, namely, the yield of the adduct (or the dehydrogenated adduct) in a reasonable time; the possibility that the true reactivity of the vinyl compound may be masked by its polymerisation or by the thermal dissociation of the adduct or by other factors, has been ignored. Among vinyl compounds this variation of activity in the Diels–Alder reaction with quinones increases the scope of this synthesis.

Experimental

M. p. determinations were made in Pyrex tubes.

2-2′-*Thienylethanol*.—A solution of 2-thienylmagnesium iodide [from 2-iodothiophen [10] (80 g.) and magnesium (11·0 g.) in ether (175 ml.)] was diluted with dry benzene (175 ml.) and cooled to −10°. Then ethylene oxide (23 g.) in ether (75 ml.) was added with stirring during 30 min. After 12 hr. the solution was distilled until the temperature of the distillate reached 70° (later vigorous decomposition may occur), then refluxed for 2 hr. The cooled solution was decomposed with dilute hydrochloric acid, and the organic layer was separated. The aqueous

[10] Minnis, *Org. Synth.*, Coll. Vol. II, p. 357.

layer was extracted with ether, and the combined extracts were evaporated and distilled, giving 2-2′-thienylethanol (39 g., 78%), b. p. 112—115°/20 mm. (lit.,[11] b. p. 99—100°/7 mm.).

2-Vinylthiophen.—2-2′-Thienylethanol (30 g.) in toluene (30 ml.) was dehydrated with molten potassium hydroxide (130 g.) as described for 3-vinylthionaphthen,[8] but at approx. 100 mm. The product was distilled, giving 2-vinylthiophen, b. p. 77—78°/70 mm. (lit.,[11] b. p. 65·5—66·5°/48 mm.) (17·0 g., 68%). Yields of 28—33% were obtained by chloroethylation of thiophen, followed by dehydrochlorination.[12] 2-Vinylthiophen, stored at 0° over a little quinol, did not polymerise materially in 6 months.

Reactions of 2-Vinylthiophen.—(1) *With p-benzoquinone.* Freshly sublimed *p*-benzoquinone (4·0 g.) and 2-vinylthiophen (1·3 g.) in acetic acid (15 ml.) were heated on the water-bath for 8 hr. The solvent was removed at reduced pressure and the residue extracted with benzene (3 × 50 ml.). The extracts were concentrated to 5 ml., and the product was extracted with cold ether (35 ml.) (to remove quinol and quinhydrone). The insoluble material was recrystallised from ethanol, giving orange needles of **4** : *5-benzothionaphthen-1′* : *4′-quinone*, m. p. 167—168° (0·88 g., 45%) (Found: C, 67·6; H, 3·0. $C_{12}H_6O_2S$ requires C, 67·3; H, 2·8%).

The quinone (0·4 g.) was extracted (Soxhlet) into lithium aluminium hydride (0·4 g.) in dry tetrahydrofuran (20 ml.) for 10 hr. The excess of hydride was decomposed with moist ether, and inorganic material was dissolved with dilute hydrochloric acid. The organic layer on evaporation gave an oil (0·31 g.) which slowly crystallised. The product from methanol gave plates of **4** : 5-benzothionaphthen, m. p. and mixed m. p. 110—111° (0·20 g., 53%).

The quinone (0·2 g.) and 3-vinylthionaphthen (0·4 g.) in acetic acid (4·0 ml.) were heated on the water-bath for 10 min., yellow crystals separating. The mixture was cooled and filtered, and the solid was washed with a little ether and recrystallised from benzene–ethanol, giving pale yellow needles of the **3** : **4** : **11** : **12**-*tetrahydrothienothionaphthenoanthraquinone* (IV) or (V), m. p. 209·5—210° (decomp.) (0·22 g., 61%) (Found: C, 70·6; H, 3·8. $C_{22}H_{14}O_2S_2$ requires C, 70·6; H, 3·7%).

(2) *With maleic anhydride.* 2-Vinylthiophen (5·0 g.), maleic anhydride (4·5 g.), and quinol (0·05 g.) in dry benzene (15·0 ml.) were refluxed for 6 hr. Crystals began to separate after 2½ hr. The precipitate from the cooled solution was washed with benzene to remove traces of viscous polymer, and the *adduct* (4·65 g.; m. p. 164—166°) analysed without further purification (Found: C, 58·2; H, 3·6. $C_{10}H_8O_3S$ requires C, 57·7; H, 3·8%). It was very insoluble in non-polar solvents and irreversibly changed by polar solvents. Thus, attempted recrystallisation from acetic acid gave fumaric acid, m. p. and mixed m. p. 284—285° (sealed tube) (Found: C, 41·4; H, 3·5. Calc. for $C_4H_4O_4$: C, 41·1; H, 3·4%).

The preceding adduct (0·8 g.) was warmed on a water-bath for 10 min. with 5N-sodium hydroxide (10 ml.). Acidification of the cooled solution gave the acid (II) (0·83 g., 96%), which crystallised from ethyl acetate in prisms, m. p. 213—214° (decomp.) (Found: C, 53·4; H, 4·7. Calc. for $C_{10}H_{10}O_4S$: C, 53·1; H, 4·4%). This acid was unchanged by refluxing acetic acid containing hydrogen chloride.

The foregoing acid (2·0 g.) and sulphur (0·7 g.) were heated at 208° for 2 hr. The product, recrystallised from carbon tetrachloride (charcoal), gave pale yellow prisms, m. p. 178—178·5°, of *thionaphthen-4* : *5-dicarboxylic anhydride* (0·62 g., 63%) (Found: C, 58·6; H, 2·3. $C_{10}H_4O_3S$ requires C, 58·8; H, 1·9%).

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UNIVERSITY OF MELBOURNE, AUSTRALIA. [*Received, July 9th*, 1957.]

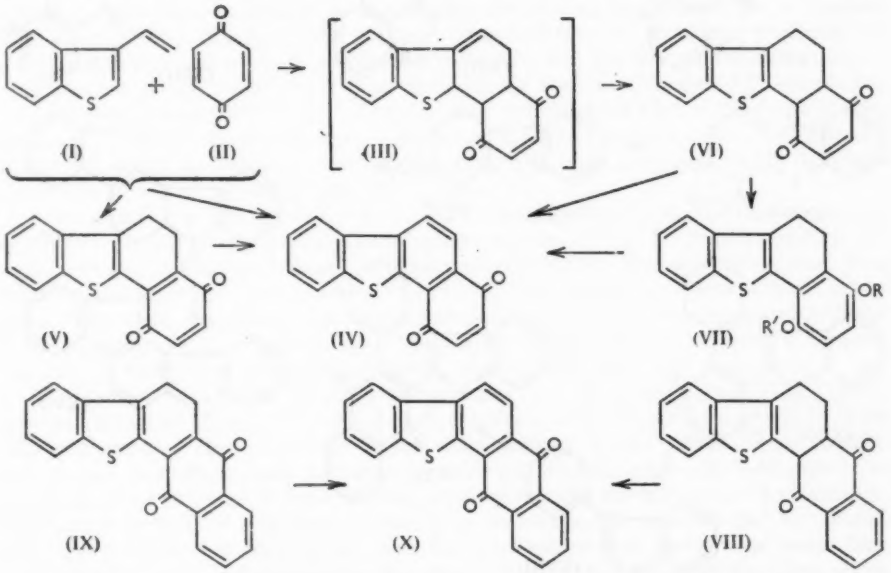
[11] Schick and Hartough, *J. Amer. Chem. Soc.*, 1948, **70**, 1646.
[12] Emerson and Patrick, *J. Org. Chem.*, 1948, **13**, 729.

992. *The Synthesis of Condensed Heterocyclic Systems. Part II.*[1] *The Use of* 3-*Vinylthionaphthen and* 3-cyclo*Hex*-1′-*enylthionaphthen in the Diene Synthesis.*

By W. Davies and Q. N. Porter.

Polycyclic thiahydrocarbons containing one thiophen and two—four benzene rings are prepared from the adducts of 3-vinylthionaphthen with maleic anhydride, *p*-benzoquinone, and 1 : 4-naphthaquinone respectively. The acetates of 2- and 5-hydroxy-1 : 4-naphthaquinone also react. From the adduct of thionaphthen 1 : 1-dioxide and 3-vinylthionaphthen a pentacyclic compound with two thiophen rings is obtained, while penta- and hexacyclic quinones containing one thiophen ring are formed from 3-*cyclo*hex-1′-enylthionaphthen with *p*-benzoquinone and 1 : 4-naphthaquinone respectively.

The ready production[2] of a naphthothiafluorene by interaction of thionaphthen 1 : 1-dioxide and 1-vinylnaphthalene suggested that the reverse type of process might be fruitful, namely, the reaction of a sulphur-containing diene with a benzenoid dienophil.



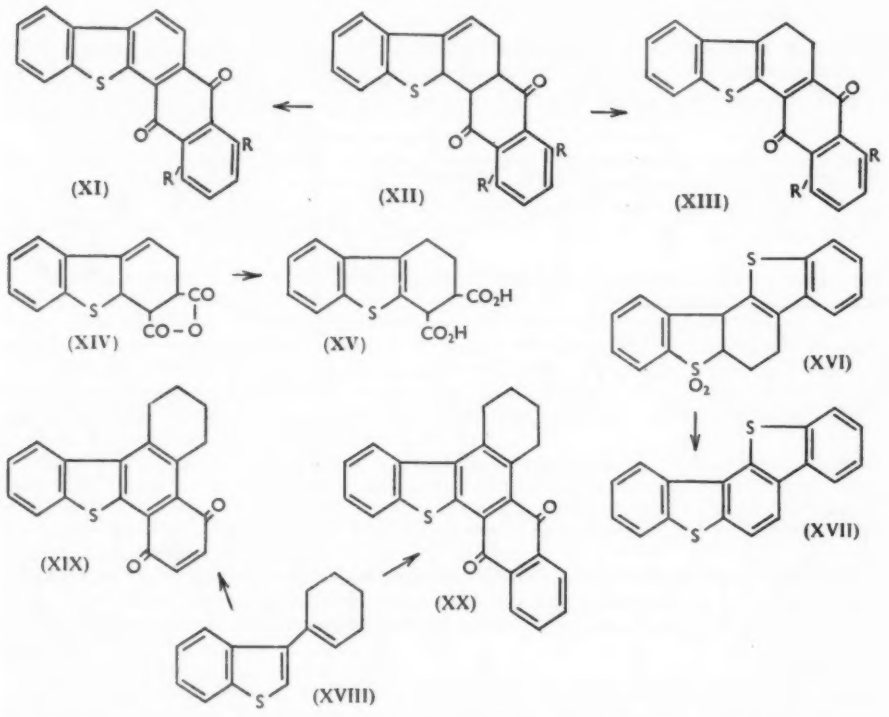
The preliminary work[1] is now amplified, chiefly with respect to reaction of 3-vinylthionaphthen with benzoquinone and with 1 : 4-naphthaquinone and some of its derivatives.

Elucidation of the structure of our partly hydrogenated products has been aided by a relation between degree of conjugation and colour, and by the effect of mineral acid, any resulting rearrangements leading to increased conjugation. Diene syntheses were carried out in acetic acid at 100° unless otherwise specified.

In reaction of 3-vinylthionaphthen (I) with an excess of benzoquinone (II) for 8 hours complete aromatisation takes place,[3] and the orange-red 9-thia-1 : 2-benzofluorene-1′ : 4′-quinone (IV) is produced. It is now found that a weaker solution, with a reaction

[1] Part I, preceding paper.
[2] Davies and Porter, *J.*, 1957, 459.
[3] Davies, Porter, and Wilmshurst, *J.*, 1957, 3366.

time of 3 hours, gives a dihydro-derivative, for which structure (V) is suggested as the red-brown colour (deep-red solution in acetic acid) indicates the presence of a quinonoid system: this product is readily dehydrogenated by chloranil to the quinone (IV). Further, an excess of vinylthionaphthen and a very short reaction time leads to a 70% yield of the pale yellow adduct (VI), which is also dehydrogenated by chloranil to the fully aromatic quinone (IV). Structure (VI) is suggested, rather than that of the theoretical first adduct (III), because the compound is not only produced in hot acetic acid, but is stable to boiling acetic acid containing hydrogen chloride, which would probably isomerise a compound (III). Another possibility is that the compound isolated is formed by enolisation of the diketone (VI), and is the quinol (VII; R = R′ = H), whose diacetate (VII; R = R′ = Ac) is formed by boiling acetic anhydride containing sulphuric acid. However, the original compound contains no hydroxyl groups—it is insoluble in cold sodium hydroxide solution



and with cold methylmagnesium iodide gives no methane: nevertheless it is potentially enolic, for it dissolves in boiling aqueous sodium hydroxide to a clear yellow solution, from which the quinone (V) is deposited. The chemical evidence for structure (VI) is supported by the infrared spectrum which shows two carbonyl (1698·2 and 1675·3 cm.$^{-1}$), but no hydroxyl, frequencies.

3-Vinylthionaphthen also reacts readily with 1 : 4-naphthaquinone. An excess of diene produces the almost colourless adduct (VIII), which, like (VI), gives negative tests for active hydrogen and enol; an excess of the quinone leads to the dark-red quinone (IX), whose benzene and acetic acid solutions are red-purple. This compound is dehydrogenated to the light brown quinone (X) by chloranil, but not by an excess of 1 : 4-naphthaquinone, a negative result which contrasts with the oxidising action of benzoquinone to

form (IV) in accord with the fact that benzoquinone is a stronger oxidant than 1 : 4-naphthaquinone.

The products (IX) and (X) give different quinol diacetates on reductive acetylation, which disposes of the possibility—not disproved by analysis—that the former is a quinhydrone. In line with this, the product (IX) contains no active hydrogen and is insoluble in boiling dilute aqueous sodium hydroxide.

Of the methods used for complete removal of oxygen from anthraquinones,[4] the most successful is reduction to the anthrone by stannous chloride,[5] followed by a modified Clemmensen reduction.[6] This technique leads also to a good yield of the fully aromatic oxygen-free compound from the quinone (X).

3-Vinylthionaphthen and juglone (5-hydroxy-1 : 4-naphthaquinone) give an adduct (XI; R = OH, R′ = H, or *vice versa*), slowly and in only 33% yield, whence juglone is not as reactive a dienophile as the parent quinone. However, even at room temperature, juglone acetate gives a 76% yield of the adduct (XII; R = OAc, R′ = H, or *vice versa*), in which migration of the double bond has not occurred (probably owing to the mild conditions employed). The adduct, in an oxidising environment, is rapidly converted by hot acetic acid containing hydrochloric acid into a stable dark red 3 : 4-dihydro-derivative (XIII; R = OAc, R′ = H, or *vice versa*), oxidation and migration of the double bond occurring. The new compound is rapidly dehydrogenated by chloranil to a quinone (XI), identical with the compound obtained by acetylation of the adduct from juglone and 3-vinylthionaphthen; thus juglone and its acetate add the diene in the same way.

Somewhat similar results have been obtained for lawsone (2-hydroxy-1 : 4-naphthaquinone) and its acetyl derivative. Lawsone does not react with 3-vinylthionaphthen in acetic acid at 100°, whereas the acetyl compound gives the quinone (X). The expected adduct containing an angular acetoxy-group apparently loses acetic acid and is dehydrogenated by excess of quinone during the reaction.

Fieser and Dunn [7] showed that with 2 : 3-dimethylbutadiene in alcohol juglone formed an adduct slightly more readily than juglone acetate. With 3-vinylthionaphthen in acetic acid the reverse is the case. It is possible that juglone does not always react as a normal naphthaquinone, since Thomson [8] has shown that it gives no hydroxyl bands in the infrared spectrum, suggesting that this is due to strong hydrogen-bonding between the 5-hydroxyl group and the neighbouring carbonyl-oxygen atom. The unreactivity of lawsone may also be partly due to hydrogen-bonding, absent from the acetyl compound.

Attention is called to the tendency in this series for 1 : 4-diketones [*e.g.*, (VI), (VIII)] to be formed rather than the isomeric dienols or quinols, even though these would be more fully conjugated. There seems to be no exact analogy among aromatic compounds, though there is a related case of isomerism in the naphthalene series: 2 : 3-dihydro-1 : 4-naphthaquinone (which is formed in small yield by heating the isomeric 1 : 4-dihydroxynaphthalene to 210° in a vacuum) is readily isomerised to the aromatic diol by mineral acid; here the quinol is more stable than the diketone, whereas the reverse seems true with our tetracyclic and pentacyclic diketones. Among derivatives of the acene series phenols tend more to form ketones as the number of rings increases: [9] however, the diketones found in our work belong to the angular series, and the carbonyl groups are not in a central ring.

Maleic anhydride and 3-vinylthionaphthen in benzene form an adduct, which, being unsaturated, is assigned structure (XIV). This rearranges in acid or alkali to the acid (XV). Aromatisation by means of selenium, followed by decarboxylation, gives dibenzothiophen.

[4] Clar, "Aromatische Kohlenwasserstoffe," Springer-Verlag, Berlin, 1952, p. 107; Campbell and Gow, *J.*, 1949, 1555; Mayer, *Annalen*, 1931, **488**, 259.
[5] Cook, *J.*, 1932, 456.
[6] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[7] Fieser and Dunn, *ibid.*, 1937, **59**, 1016.
[8] Thomson, *J.*, 1950, 1737.
[9] Ref. 4, p. 18.

3-Vinylthionaphthen and thionaphthen 1 : 1-dioxide in toluene afford a 65% yield of the tetrahydro-derivative (XVI), which is converted by lithium aluminium hydride followed by selenium into the fully aromatic compound (XVII). Desulphurisation of this gives *m*-terphenyl, whereas the possible primary adduct other than (XVI) would have led to *p*-terphenyl (αβ-addition of the diene being assumed).

3-*cyclo*Hex-1′-enylthionaphthen (XVIII) has been shown [10] to react as a diene with maleic anhydride. It is now found with benzoquinone and 1 : 4-naphthaquinone it gives the adducts (XIX) and (XX) which are crimson and light orange respectively. In both cases dehydrogenation has occurred even in the presence of excess of diene; this does not affect the *cyclo*hexene rings since the two products contain neither active hydrogen nor acidic centres. Moreover the structure (XX) is supported by the infrared spectroscopy. So far it has not proved possible to remove the oxygen from these quinones.

Experimental

M. p. determinations were made in Pyrex tubes.

Dienes.—3-Vinylthionaphthen (I), b. p. 138—140°/18 mm., was prepared as before,[3] and also from 3-2′-bromoethylthionaphthen, of which 35 g. were refluxed for 30 min. with potassium hydroxide (8·75 g.) in 95% ethanol (330 ml.), cold diluted solution yielding to benzene 3-vinylthionaphthen (19 g., 81%), b. p. 133—134°/25 mm. The overall yield (62%) from 3-2′-hydroxyethylthionaphthen is higher than that from the previous process. The alcohol (obtained from 3-thionaphthenylmagnesium bromide and acetaldehyde), when distilled from potassium hydrogen sulphate, gave a 10% yield of 3-vinylthionaphthen and much polymer.

3-*cyclo*Hex-1′-enylthionaphthen (XVIII), b. p. 177—181°/2 mm., was prepared [10] (66%) by interaction of *cyclo*hexanone and 3-thionaphthenylmagnesium bromide, followed by dehydration.

Reaction of 3-Vinylthionaphthen with Benzoquinone.—(i) *p*-Benzoquinone (0·86 g., 0·008 mole) and 3-vinylthionaphthen (0·32 g., 0·002 mole) in glacial acetic acid (10·0 ml.) were heated on the water-bath for 3 hr. and the product, which separated on cooling, was washed with ether to remove quinhydrone. The brown residue recrystallised from benzene, giving brown needles (0·36 g., 66%) of 3 : 4-*dihydro*-9-*thia*-1 : 2-*benzofluorene*-1′ : 4′-*quinone* (V), m. p. 202—202·5° [mixed m. p. with the quinone (IV), 185—187°] (Found: C, 71·85; H, 3·8. $C_{16}H_{10}O_2S$ requires C, 72·20; H, 3·8%). The product was stable for 30 min. in boiling acetic acid containing hydrogen chloride.

(ii) Benzoquinone (1·08 g., 0·001 mole) and 3-vinylthionaphthen (2·4 g., 0·0015 mole) in acetic acid (40 ml.) were heated on the water-bath for 10 min., and after 1 hr. at room temperature the yellow precipitate was recrystallised from benzene, giving yellow needles (1·9 g., 69%) of 1 : 2 : 3 : 4-*tetrahydro*-9-*thia*-1 : 2-*benzofluorene*-1′ : 4′-*quinone* (VI), m. p. 206—207°, unchanged when refluxed for 30 min. in acetic acid saturated with hydrogen chloride (Found: C, 71·7; H, 4·6. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5%). No increase in yield occurred when the molar ratio was greater than 1·5. When equimolecular quantities of quinone and vinyl compound were treated under the above conditions, the yield fell to 55%.

Proof of the Structure (VI).—This diketone was converted by warm acetic anhydride containing a little concentrated sulphuric acid into 1′ : 4′-*diacetoxy*-3 : 4-*dihydro*-9-*thia* 1 : 2-*benzofluorene* (VII; R = R′ = Ac), colourless prisms (from benzene), m. p. 209—210° (Found: C, 68·35; H, 4·3. $C_{20}H_{14}O_4S$ requires C, 68·2; H, 4·0%). Our test for active hydrogen was instantaneous brisk evolution of gas when a cold solution of the compound in anisole was mixed with a cold solution of ethereal methylmagnesium iodide. It was negative with compound (VI). The compound was insoluble in cold sodium hydroxide solution. Boiling aqueous sodium hydroxide at once formed a deep yellow solution which soon became brown and gave a precipitate which recrystallised from glacial acetic acid in brown needles of compound (V), m. p. and mixed m. p. 201·5—202·5°.

Dehydrogenation of Compounds (V) *and* (VI).—Compound (VI) (0·1 g.) and chloranil (0·2 g.) in xylene (5·0 ml.) were refluxed for 8 hr., and the crystalline product from the cold solution was washed with ether and recrystallised from benzene, giving orange-red needles of 9-thia-1 : 2-benzofluorene-1′ : 4′-quinone, m. p. and mixed m. p. 197—198°. The compound (V) (0·1 g.) with chloranil (0·1 g.) gave the same quinone.

[10] Szmuszkovicz and Modest, *J. Amer. Chem. Soc.*, 1950, **72**, 571.

Reaction of 3-*Vinylthionaphthen with* 1 : 4-*Naphthaquinone*.—(i) The quinone [11] (m. p. 124—125°; 0·32 g., 0·002 mole) and 3-vinylthionaphthen (0·48 g., 0·003 mole) in glacial acetic acid (5·0 ml.) were heated on the water-bath for 10 min., then cooled for 1 hr. The yellow crystalline product recrystallised from benzene in pale yellow needles (0·4 g., 63%) of 1 : 2 : 3 : 4-*tetrahydronaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (VIII), m. p. 209—210° (Found: C, 75·65; H, 4·6. $C_{20}H_{14}O_2S$ requires C, 75·45; H, 4·4%). It was unaffected for a short time in refluxing acetic acid containing hydrogen chloride, and gave no methane with methylmagnesium iodide. It gave a red solution in boiling dilute aqueous sodium hydroxide.

(ii) 3-Vinylthionaphthen (1·6 g., 0·001 mole) and 1 : 4-naphthaquinone (4·8 g., 0·003 mole) in acetic acid (50 ml.) were heated on the water-bath for 10 hr. and the dark-red crystals from the cold solution washed with ether and recrystallised from glacial acetic acid, giving dark red needles (2·2 g., 70%) of 3 : 4-*dihydronaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (IX), m. p. 217—218° (Found: C, 76·1; H, 3·85. $C_{20}H_{12}O_2S$ requires C, 75·9: H, 3·8%), somewhat soluble in anisole and insoluble in dilute aqueous sodium hydroxide when boiled for a short time; the dark red anisole solution gives no methane with methylmagnesium iodide.

1′ : 4′-*Diacetoxy*-3 : 4-*dihydronaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*, needles (from benzene), m. p. 253—254°, was formed by reduction with zinc dust and anhydrous sodium acetate in acetic anhydride (Found: C, 71·6; H, 4·74. $C_{24}H_{18}O_4S$ requires C, 71·6; H, 4·5%).

Naphtho(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (X), pale brow nneedles, m. p. 273—274°, was formed (0·11 g.) when the compound (IX) (0·16 g.) and chloranil (0·13 g.) in xylene (10·0 ml.) were refluxed for 10 hr. It separated on cooling and recrystallised from acetic acid (Found: C, 76·1; H, 3·3. $C_{20}H_{10}O_2S$ requires C, 76·4; H, 3·2%). Its reductive acetylation gave 1′ : 4′-*diacetoxy*-9-*thianaphtho*(2′ : 3′-1 : 2)*fluorene*, pale yellow prisms (from benzene), m. p. 310—311° (Found: C, 71·7; H, 4·2. $C_{24}H_{16}O_4S$ requires C, 72·0; H, 4·0%).

Reduction of Naphtho(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone*.—To the quinone (X) (0·3 g.), suspended in refluxing glacial acetic acid (50 ml.), was added dropwise (10 min.) a solution of stannous chloride (1·2 g.) in concentrated hydrochloric acid (6·0 ml.). Refluxing was continued until the quinone was completely dissolved (2 hr.). The cold solution deposited the *anthrone*, which crystallised from benzene in orange prisms (0·15 g., 51%), m. p. 208—210° (Found: C, 79·7; H, 3·1. $C_{20}H_{12}OS$ requires C, 80·0; H, 4·0%). It (0·1 g.) was refluxed for 10 hr. with zinc dust (0·4 g.) (which had been treated with 0·1% copper sulphate solution for 5 min.) in 2N-sodium hydroxide (10 ml.) under toluene (5 ml.). The toluene layer was separated, the aqueous layer extracted once with benzene, and the residue from the combined extracts crystallised from benzene (charcoal), giving cream plates (0·05 g., 53%) of *naphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*, m. p. 226—226·5° (Found: C, 84·5; H, 4·4. $C_{20}H_{12}S$ requires C, 84·5; H, 4·2%).

Reaction of 3-*Vinylthionaphthen with Other Quinones*.—(*a*) Juglone (2·0 g.) and 3-vinylthionaphthen (1·0 g.) in acetic acid (10·0 ml.) were heated on the water-bath for 6 hr., and the ether-washed product from the cold solution recrystallised from benzene in deep-red needles (0·75 g., 33%) of 5′(or 8′)-*hydroxynaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (XI), m. p. 267—268° (decomp.) (Found: C, 72·3; H, 3·8. $C_{20}H_{12}O_3S$ requires C, 72·3; H, 3·6%).

When this quinone (0·06 g.) in acetic anhydride (2·0 ml.) containing pyridine (2 drops) was heated on the water-bath for 4 hr., the colour changed from deep-red to pale yellow. The crystals from the cold solution recrystallised from benzene in yellow needles of the *acetate*, m. p. 288—289° (decomp.) (Found: C, 71·0; H, 3·5. $C_{22}H_{12}O_4S$ requires C, 70·9; H, 3·2%).

(*b*) Juglone acetate [7] (0·5 g.), dissolved in acetic acid (7·0 ml.), was added to 3-vinylthionaphthen (0·5 g.) in acetic acid (2·0 ml.) at room temperature. Pale yellow crystals began to separate after 10 min. The solution was kept overnight, then filtered, giving yellow needles (0·66 g., 76%), m. p. 206—207°. Long heating in acetic acid gave a red colour and a less pure product, but rapid recrystallisation from acetic acid gave pale yellow needles of 1 : 2 : 3 : 10-*tetrahydro*-5′(*or* 8′)-*acetoxynaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (XI), m. p. 209—210° (Found: C, 69·6; H, 4·3; O, 17·2; S, 8·5. $C_{22}H_{16}O_4S$ requires C, 70·2; H, 4·2; O, 17·0; S, 8·5%). It is readily soluble in anisole, and has no active hydrogen, it is insoluble in cold aqueous sodium hydroxide, but in boiling alkali gives a red solution.

5′(*or* 8′)-*Acetoxy*-3 : 4-*dihydronaphtho*(2′ : 3′-1 : 2)-9-*thiafluorene*-1′ : 4′-*quinone* (XIII) (0·08 g.) separated in two weeks on exposure to air of the mother-liquors from the above adduct, and crystallised from anisole or acetic acid in red-purple needles, m. p. 294—295°, which have no

[11] Fieser, *Org. Synth.*, Coll. Vol. II, p. 430; Coll. Vol. I, p. 383; Braude and Fawcett, *ibid.*, Vol. XXXIII, p. 50.

active hydrogen (Found: C, 70·8; H, 3·7. $C_{22}H_{14}O_4S$ requires C, 70·6; H, 3·7%). It is more readily prepared (70% yield) by atmospheric oxidation of the hydrolysate obtained by refluxing for about ½ hr. the adduct (XII) with boiling acetic acid containing a little concentrated hydrochloric acid. This oxidation with benzoquinone is immediate. The adduct (XII) (0·25 g.) and chloranil (0·36 g.) in xylene (8·0 ml.) were refluxed until a copious yellow precipitate separated (10 min.). The product (XI; R = OAc, R′ = H or *vice versa*) recrystallised from xylene in yellow needles (0·21 g., 85%), m. p. and mixed m. p. 289·5—290° (Found: C, 71·2; H, 3·4; S, 8·6. Calc. for $C_{22}H_{12}O_4S$: C, 70·9; H, 3·2; S, 8·6%).

(*c*) Lawsone acetate [12] (0·25 g.) and 3-vinylthionaphthen (0·25 g.) in acetic acid (2·5 ml.) were heated on the water-bath for 4 hr., and the product recrystallised from acetic acid, in pale-brown needles (0·15 g.) of naphtho(2′ : 3′-1 : 2)-9-thiafluorene-1′ : 4′-quinone (X), m. p. and mixed m. p. 270—271° (Found: C, 75·9; H, 3·4. Calc. for $C_{20}H_{10}O_2S$: C, 76·4; H, 3·2%). Lawsone itself was recovered when treated with 3-vinylthionaphthen under these conditions.

Reaction of 3-*Vinylthionaphthen with Maleic Anhydride.*—3-Vinylthionaphthen (3·2 g.) and maleic anhydride (2·0 g.) in dry benzene (35 ml.) containing quinol (0·05 g.) were refluxed for 6 hr. (water-bath). Colourless plates of 2 : 3 : 4 : 12-*tetrahydrodibenzothiophen*-3 : 4-*dicarboxylic anhydride* (XIV), m. p. 194—195°, separated on cooling (Found: C, 64·7; H, 4·1. $C_{14}H_{10}O_3S$ requires C, 65·1; H, 3·9%). This is rapidly decomposed to soluble products by boiling acetic acid. Its chloroform solution immediately decolorised a dilute solution of bromine.

The adduct (0·25 g.) was refluxed for 30 min. in acetic anhydride (2·5 ml.) and acetic acid (2·5 ml.) saturated with hydrogen chloride. The solution was cooled and diluted with ice water. The precipitate recrystallised from ethyl acetate in prisms (0·20 g.) of 1 : 2 : 3 : 4-*tetrahydrodibenzothiophen*-3 : 4-*dicarboxylic acid* (XV), m. p. 236—237° (Found: C, 61·1; H, 4·4. $C_{14}H_{12}O_3S$ requires C, 60·9; H, 4·3%). Bromine in chloroform did not decolorise the acid, which is also obtained by brief treatment of the above adduct with hot dilute sodium hydroxide solution.

A mixture of the original adduct (0·8 g.) and selenium (0·6 g.) was heated at 300—305° in a cold-finger sublimation apparatus for 6 hr., and the crystalline sublimate recrystallised from carbon tetrachloride in pale yellow needles (0·53 g.) of *dibenzothiophen*-3 : 4-*dicarboxylic anhydride*, m. p. 288—289° (Found: C, 66·0; H, 2·6. $C_{14}H_6O_3S$ requires C, 66·1; H, 2·4%). This anhydride (0·25 g.), mixed with barium hydroxide (1·0 g.) and copper bronze (0·3 g.), was heated in the sublimation apparatus at 30 mm., the temperature being slowly raised from 180° to 350° (35 min.) and kept at 350° for 30 min. The yellow sublimate was recrystallised twice from ethanol (charcoal), giving dibenzothiophen (0·03 g.), m. p. and mixed m. p. 99—100°.

Reaction of 3-*Vinylthionaphthen with Thionaphthen* 1 : 1-*Dioxide.*—The dioxide (0·5 g.), 3-vinylthionaphthen (1·0 g.), and quinol (20 mg.) were refluxed in toluene (4·0 ml.) for 8 hr. The product recrystallised from benzene in prisms (0·64 g., 65%) of 1 : 2 : 5 : 6-*tetrahydrodithionaphtheno*(2′ : 3′-1 : 2)(2″ : 3″-3 : 4)*benzene* 1′ : 1′-*dioxide* (XVI), m. p. 263—264° (Found: C, 66·5; H, 4·4; S, 19·3. $C_{18}H_{14}O_2S_2$ requires C, 66·3; H, 4·3; S, 19·6%).

This sulphone (1·0 g.) was extracted from a Soxhlet thimble with tetrahydrofuran (100 ml.) on to a solution of lithium aluminium hydride (1·0 g.) for 10 hr. The excess of hydride was decomposed as usual, and the dried organic layer evaporated, giving a pale brown oil (0·87 g.), which was heated with selenium (0·9 g.) at 310—315° for 7 hr. The cooled mixture was extracted with benzene, and the solution was decolorised (charcoal), yielding *dithionaphtheno*-(2′ : 3′-1 : 2)(2″ : 3″-3 : 4)*benzene* (XVII), needles (0·65 g.) [from light petroleum (b. p. 60—80°)], m. p. 165·5—166° (Found: C, 74·1; H, 3·5. $C_{18}H_{10}S_2$ requires C, 74·5; H, 3·4%). This (0·4 g.) was refluxed with Raney nickel (3·5 g.) in ethanol (100 ml.) for 10 hr.; filtration and concentration gave *m*-terphenyl (0·17 g.), m. p. and mixed m. p. 88—89°, undepressed when admixed with a genuine sample.

Reactions of 3-cyclo*Hex*-1′-*enylthionaphthen.*—(i) 3-*cyclo*Hex-1′-enylthionaphthen (XVIII) (2·1 g.) and *p*-benzoquinone (4·3 g.) were heated in acetic acid (20 ml.) on the water-bath for 9 hr., and the precipitate formed on cooling was washed with ethanol and recrystallised (from benzene or anisole), giving crimson needles (2·4 g., 75%) of 5′ : 6′ : 7′ : 8′-*tetrahydrophenanthra*-(9′ : 10′-2 : 3)*thionaphthen*-1′ : 4′-*quinone* (XIX), m. p. 268—269°. This has no active hydrogen atom and is not attacked on brief boiling with aqueous-alcoholic sodium hydroxide (Found: C, 75·5; H, 4·6. $C_{20}H_{14}O_2S$ requires C, 75·4; H, 4·4%). The same compound resulted (25%)

[12] Macbeth, Price, and Winzor, *J.*, 1935, 334.

from the similar interaction of 1 mol. of *p*-benzoquinone with 1·5 mol. of 3-*cyclo*hex-1′-enylthionaphthen.

(ii) 1 : 4-Naphthaquinone (2·4 g.) and 3-*cyclo*hex-1′-enylthionaphthen (1·0 g.) in acetic acid (12·0 ml.) at 100° during 6 hr. gave, on cooling, a very sparingly soluble precipitate of the *quinone* (XX), which recrystallised from benzene in orange needles (1·1 g., 61%), m. p. 320—321° (Found: C, 78·5; H, 4·6. $C_{24}H_{16}O_2S$ requires C, 78·3; H, 4·3%). This was similarly produced (19%) in 20 min. when excess of the thionaphthen was used. It has no active hydrogen, is not attacked by brief boiling with aqueous-alcoholic sodium hydroxide, and is recovered unchanged after 70 minutes' refluxing in acetic acid containing hydrochloric acid. Associate Professor A. N. Hambly reports that the infrared spectrum gives strong support to the structure (XX) " in that the methylene absorption is the strongest absorption in the C–H stretching region, while the carbonyl bond is single as found with quinones and not double as found with diketones."

This quinone was not reduced to the anthrone by stannous chloride and hydrochloric acid in boiling acetic or propionic acid, or by copper-coated zinc dust in boiling 2N-sodium hydroxide.

The authors are indebted to Dr. F. L. Winzor for a specimen of lawsone, Associate Professor A. N. Hambly for infrared-spectral determinations, Mr. R. G. Cooke for helpful discussions, the Anti-Cancer Council of Victoria for financial aid, and Monsanto Chemicals (Aust.) for a scholarship (to Q. N. P.). The microanalyses were made by Dr. W. Zimmerman and his staff.

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993. *The Synthesis of Polycyclic Aromatic Compounds. Part I. The Reaction of Quinones with Vinylnaphthalenes and Related Dienes.*

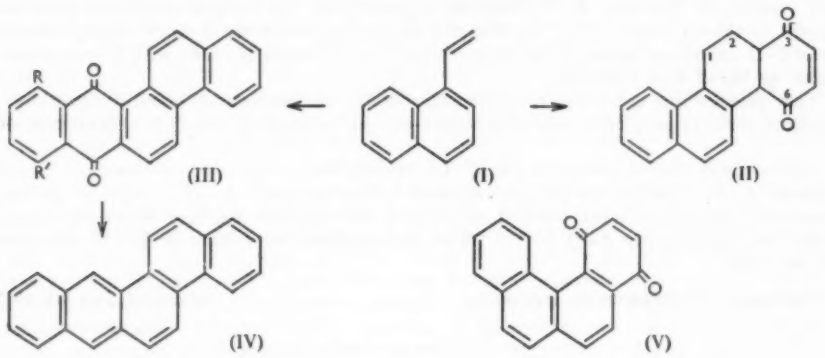
By W. DAVIES and Q. N. PORTER.

Convenient syntheses are described of chrysene-1 : 4-quinone, 3 : 4-benzophenanthrene-1′ : 4′-quinone, and naphtho(2′ : 1′-1 : 2)anthracene-9 : 10 quinone, and of the corresponding aromatic hydrocarbons. A practical advance is the direct removal, by lithium aluminium hydride, of the oxygen atoms in a quinone group in an outermost ring, to afford the aromatic hydrocarbon.

POLYCYCLIC aromatic compounds are often made starting from an aliphatic diene and a *p*-quinone (*e.g.*, butadiene and 1 : 4-naphthaquinone [1,2]) or from a vinylaromatic diene and an aliphatic dieneophil (*e.g.*, 1-vinylnaphthalene and maleic anhydride [2,3]), but there are few records of interaction of vinyl aromatic dienes with quinones prior to our use [4] of 2-vinylthiophen and 3-vinylthionaphthen. A known instance of such a reaction in the aromatic series is that [5] between 1-vinylnaphthalene (I) and *p*-benzoquinone to give a high yield of chrysene-1 : 4-quinone, excess of quinone having oxidised the original adduct (II) which was not isolated. It is now found that this pale yellow compound can be isolated if excess of 1-vinylnaphthalene is warmed with *p*-benzoquinone in glacial acetic acid for a short time and then kept for some days: it is formed much more slowly than the corresponding adduct from the isosteric 3-vinylthionaphthen and benzoquinone.[4] The adduct (II) is easily dehydrogenated by benzoquinone or chloranil to chrysene-3 : 6-quinone, which is reduced in one operation and in high yield (70%) to chrysene by lithium aluminium hydride (cf. ref. 4).

[1] Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2337.
[2] Cf. Norton, *Chem. Rev.*, 1942, **31**, 319; Kloetzel, " Organic Reactions," Wiley, New York, 1954, Vol. IV, p. 1; Holmes, *op. cit.*, p. 60; Butz and Rytina, *op. cit.*, Vol. V, p. 136.
[3] Cohen and Warren, *J.*, 1937, 1315.
[4] Davies and Porter, preceding papers; Davies, Porter, and Wilmshurst, *J.*, 1957, 3366.
[5] Bachmann and Deno, *J. Amer. Chem. Soc.*, 1949, **71**, 3062.

Although 2-vinylnaphthalene is known [3] to give an adduct with maleic anhydride, it was apparently not known to react with quinones. With excess of *p*-benzoquinone, however, 3 : 4-benzophenanthrene-1′ : 4′-quinone (V) is produced in 47% yield. The intermediate hydrogenated adduct could not be isolated, the reaction is slower than that with 1-vinylnaphthalene, and the product is more coloured (bright red) than any quinone derived from 1-vinylnaphthalene. Fischer atomic models indicate that 3 : 4-benzophenanthrene-1′ : 4′-quinone is considerably strained owing to the proximity of the



1′-oxygen atom to the neighbouring six-membered ring and it seems unlikely that the molecule is planar. Steric hindrance is probably responsible for the lower yield of adduct in this case, and for the relatively low (50%) yield of 3 : 4-benzophenanthrene formed by the reduction of the quinone with lithium aluminium hydride. No adduct has so far been isolated after reaction of 2-vinylnaphthalene and 1 : 4-naphthaquinone, the only product being 2 : 2′-dinaphthyl-1 : 4 : 1′ : 4′-diquinone, previously isolated from 1 : 4-naphthaquinone and acetic acid containing pyridine.[6]

The synthetical value of this process is seen in the preparation of naphtho(2′ : 1′-1 : 2)-anthracene-9 : 10-quinone (III; R = R′ = H) and thence by our general methods naphtho(2′ : 1′-1 : 2)anthracene (IV), previous syntheses [7] of which are less satisfactory in yield, convenience, or lack of ambiguity.

Juglone reacts with 3-vinylthionaphthen, but not with 1-vinylnaphthalene; its acetyl derivative, however, on prolonged heating gives the adduct (III; R = OAc, R′ = H, or *vice versa*) (cf. the ready reaction with 3-vinylthionaphthen [4]). The same trend is seen in the inactivity of the acetate of lawsone (2-hydroxy-1 : 4-naphthaquinone) towards 1-vinylnaphthalene, though it reacts with 3-vinylthionaphthen.[4] This difference is probably due to the lower aromaticity of 3-vinylthionaphthen. It is of interest that all the polycyclic quinones from 3-vinylthionaphthen are considerably paler than the isosteric quinones from 3-vinylthionaphthen.

1-*cyclo*Hex-1′-enylnaphthalene is stated [8] not to give an adduct with maleic anhydride, and its 3′- and 4′-methyl derivatives are reported not to react with benzoquinone.[9] It is now found that with excess of *p*-benzoquinone in acetic acid, 1-*cyclo*hex-1′-enylnaphthalene is dehydrogenated to 1-phenylnaphthalene and no adduct is formed, as previously found for reaction with chloranil.[10] No adducts were isolated on treatment of *p*-benzoquinone

[6] Rosenhauer, Braun, Pummerer, and Riegelbauer, *Ber.*, 1937, **70**, 2281.
[7] Clar, *Ber.*, 1929, **62**, 1574; Buu-Hoï, Hoan, and Jacquignon, *J.*, 1951, 1381; Martin, *Bull. Soc. chim. belges*, 1949, **58**, 87.
[8] Bergmann and Bergmann, *J. Amer. Chem. Soc.*, 1940, **62**, 1699.
[9] Bergmann and Weitzmann, *J. Org. Chem.*, 1944, **9**, 352.
[10] Arnold, Collins, and Zenk, *J. Amer. Chem. Soc.*, 1940, **62**, 983.

(3—4 mols.) in acetic acid at 100° with styrene, 1-propenylnaphthalene, or 1-*iso*propenylnaphthalene, although in each case considerable quantities of quinhydrone (dehydrogenation) and polymer were formed; it is possible that partial dehydrogenation of the polymer by benzoquinone accounts for the quinhydrone formed.

The one-stage reduction of quinones to hydrocarbons by lithium aluminium hydride [4] failed except when the quinone grouping was on the outermost ring and unfortunately even then the reaction is sometimes subject to steric effects which hinder or even prevent it.

Experimental

M. p. determinations were made in Pyrex tubes.

Reaction of 1-*Vinylnaphthalene and Benzoquinone.*—(*a*) *p*-Benzoquinone (0·3 g.) and 1-vinylnaphthalene [11] (1·0 g.) were kept at 80° for 15 min., then at room temperature for 5 days, and the crystalline product was recrystallised from benzene–ligroin, giving yellow prisms of 1 : 2 : 2*a* : 6*a*-*tetrahydrochrysene*-3 : 6-*quinone* (II) (0·25 g.), m. p. 188—189° (decomp.) (Found: C, 82·0; H, 5·0. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%).

This quinone was converted into chrysene-3 : 6-quinone, m. p. and mixed m. p. 213—214°, when heated with benzoquinone (3 mol.) in acetic acid at 100° for 4 hr., or refluxed with chloranil (2·1 mol.) in xylene for 30 min.

(*b*) 1-Vinylnaphthalene (1·5 g.) and *p*-benzoquinone (4·0 g.) in acetic acid (50 ml.) were heated on the water-bath for 5 hr., then cooled, and the precipitate recrystallised from acetic acid in orange needles of chrysene-3 : 6-quinone, m. p. 213·5—214° (2·0 g., 77%) (Bachmann and Deno [5] report m. p. 206·5—207·5° and 78% yield (Found: C, 83·5; H, 3·95. Calc. for $C_{18}H_{10}O_2$: C, 83·7; H, 3·9%).

Reduction of Chrysene-3 : 6-*quinone.*—The quinone (0·88 g.) was extracted (Soxhlet) into a solution of lithium aluminium hydride (1·0 g.) in boiling tetrahydrofuran (150 ml.) for 10 hr. The excess of hydride was decomposed with moist ether, and dilute hydrochloric acid added; the dried ethereal layer yielded a yellow solid (0·7 g.) which on recrystallisation from acetic acid (charcoal) gave chrysene (0·55 g., 70%), m. p. and mixed m. p. 253—254° (Found: C, 94·4; H, 5·4. Calc. for $C_{18}H_{12}$: C, 94·7; H, 5·3%).

Reaction of 2-*Vinylnaphthalene with* p-*Benzoquinone.*—2-Vinylnaphthalene [11] (1·5 g.) and *p*-benzoquinone (4·0 g.) in acetic acid (30 ml.) were heated on the water-bath for 12 hr. and the black needles, deposited on cooling, were washed with cold ethanol to remove quinhydrone. The residue recrystallised from acetic acid in red needles of 3 : 4-*benzophenanthrene*-1′ : 4′-*quinone* (V), m. p. 229·5—230° (1·42 g., 37%) (Found: C, 83·4; H, 3·9%). It (0·5 g.) was reduced with lithium aluminium hydride as described for chrysenequinone, giving 3 : 4-benzophenanthrene, needles (from ethanol), m. p. 67·5—68° (lit.,[12] m. p. 68°) (0·23 g., 50%) (Found: C, 94·6; H, 5·3%).

Reaction of 1-*Vinylnaphthalene and* 1 : 4-*Naphthaquinone.*—The quinone (6·0 g.) and 1-vinylnaphthalene (2·0 g.) in acetic acid (50 ml.) were heated on the water-bath for 5 hr., and the precipitate formed on cooling was recrystallised from xylene, giving pale-yellow needles of naphtho(2′ : 1′-1 : 2)anthracene-9 : 10-quinone (III; R = R′ = H), m. p. 288—288·5° (lit.,[7] m. p. 269—270°) (3·4 g., 74%) (Found: C, 85·55; H, 4·0. Calc. for $C_{22}H_{12}O_2$: C, 85·7; H, 3·9%).

This quinone (0·2 g.), zinc dust (0·4 g.), and anhydrous sodium acetate (0·2 g.) were refluxed in acetic anhydride (10 ml.) for 30 min. The solution was added to water (100 ml.), and the product recrystallised from benzene, giving pale cream needles of 9 : 10-*diacetoxynaphtho*(2′ : 1′-1 : 2)*anthracene*, m. p. 273—274° (0·17 g.) (Found: C, 79·1; H, 4·8. $C_{26}H_{18}O_4$ requires C, 79·1; H, 4·6%).

Naphtho(2′ : 1′-1 : 2)*anthracene* (IV).—The preceding quinone (1·0 g.) in refluxing acetic acid (150 ml.) was treated dropwise with stannous chloride (4·0 g.) in concentrated hydrochloric acid (10 ml.), and the mixture then refluxed for 1½ hr., concentrated to 100 ml., and cooled. The product that separated recrystallised from benzene, giving yellow prisms of the *anthrone*, m. p. 227—228° (0·73 g.) (Found: C, 89·8; H, 4·8. $C_{22}H_{14}O$ requires C, 89·8; H, 4·8%).

The anthrone (0·5 g.) and zinc dust activated by brief treatment with 0·1% copper sulphate solution were refluxed in 2N-sodium hydroxide (25 ml.) under toluene (10 ml.) for 12 hr. Extra

[11] Davies and Porter, *J.*, 1957, 459.
[12] Cook, *J.*, 1931, 2524.

XUM

toluene (50 ml.) was added and the aqueous phase separated from the hot solution. The toluene layer was decolorised (charcoal) and concentrated, giving pale cream plates of naphtho(2′ : 1′-1 : 2)anthracene, m. p. 303—304° (0·47 g.) (lit.,[7] m. p. 293—294°) (Found: C, 94·8; H, 5·05. Calc. for $C_{22}H_{14}$: C, 95·0; H, 5·0%).

The hydrocarbon was also produced (65%) by reducing the quinone directly by the modified Clemmensen reduction,[13] without first forming the anthrone.

Reaction of 2-*Vinylnaphthalene and* 1 : 4-*Naphthaquinone*.—The quinone (3·0 g.) and 2-vinylnaphthalene (1·0 g.) in acetic acid (20 ml.) were heated on the water-bath for 12 hr. The product that separated recrystallised from benzene as yellow needles (0·9 g.), m. p. 271—273° (decomp.: darkening at 240°) (Found: C, 76·2; H, 3·3. Calc. for $C_{20}H_{10}O_4$: C, 76·4; H, 3·2%). Rosenhauer *et al.*[6] report m. p. 274—275° (decomp.) for 2 : 2′-dinaphthyl-1 : 4-1′ : 4′-diquinone.

Reaction of 1-*Vinylnaphthalene with Juglone Acetate*.—The quinone (2·5 g.) and 1-vinylnaphthalene (0·8 g.) in acetic acid (15 ml.) were heated on the water-bath for 8 hr. The product crystallised from benzene, giving yellow needles of 5′(or 8′-)*acetoxynaphtho*(2′ : 1′-1 : 2)*anthracene* (III; R = H, R′ = OAc, or *vice versa*), m. p. 268—269° (0·92 g.) (Found: C, 78·7; H, 3·6. $C_{24}H_{14}O_4$ requires C, 78·8; H, 3·8%).

Reaction of 1-cyclo*Hex*-1′-*enylnaphthalene and Benzoquinone*.—The quinone (4·5 g.) and 1-*cyclo*hex-1′-enylnaphthalene (3·0 g.) were heated in acetic acid (60 ml.) on the water-bath for 12 hr. Quinhydrone, m. p. and mixed m. p. 171°, separated on cooling. The filtrate was evaporated under reduced pressure (water-bath), excess of benzoquinone removed by sublimation, and the residue steam-distilled. The distillate, extracted with ether, gave 1-phenylnaphthalene (1·6 g.), b. p. 186—188°/22 mm. (no picrate; 4-bromo-derivative,[14] m. p. 75—76°).

The authors thank Mr. J. R. Wilmshurst for assistance, the Anti-Cancer Council of Victoria for financial aid, and Monsanto Chemicals (Australia) for a scholarship (to Q. N. P). The microanalyses were carried out by Dr. W. Zimmermann and his staff.

UNIVERSITY OF MELBOURNE, AUSTRALIA. [*Received, July 9th*, 1957.]

[13] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[14] Weiss and Woiditch, *Monatsh.*, 1925, **46**, 453.

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994. *Nucleophilic Substitution Reactions of Benzyl Halides. Part II.* Rates and Product Proportions for the Solvolysis of Benzyl Chloride in Ethanol–Water Mixtures.*

By G. KOHNSTAM and P. R. ROBINSON.

The proportions of the two reaction products for the ethanolysis-hydrolysis of benzyl chloride differ considerably from those required by the Olson–Halford equation.[1] This is explained in terms of the sensitivity of the transition-state structures to changes in the solvent composition.

THIS paper reports overall rates and the proportions of the two reaction products for the solvolysis of benzyl chloride in a number of ethanol–water mixtures. Hughes, Ingold, and their co-workers have shown that Olson and Halford's fugacity rate equation[1] accurately predicts the product proportions in the alcoholysis-hydrolysis of *n*-butyl bromide,[2] which occurs by the more extreme form of the bimolecular mechanism (S_N2), but not in the corresponding reactions of *tert.*-butyl chloride[3] where the unimolecular mechanism (S_N1) is operating. Nucleophilic displacements in benzyl chloride take place in a manner intermediate between the extreme bimolecular and unimolecular mechanisms, at least in partly aqueous solvents, and it was of interest to examine the validity of this equation under such conditions.

* Part I, *J.*, 1957, 4747.

[1] Olson and Halford, *J. Amer. Chem. Soc.*, 1937, **59**, 2644.
[2] Bird, Hughes, and Ingold, *J.*, 1943, 255.
[3] Bateman, Hughes, and Ingold, *J.*, 1938, 881.

For the ethanolysis-hydrolysis of an organic chloride, RCl, Olson and Halford's equation takes the form

$$d[ROH]/dt = k_w p_w p_{RCl},\ d[ROEt]/dt = k_e p_e p_{RCl}$$

where the k's are the fugacity rate coefficients which are independent of the solvent composition, the p's are the partial vapour pressures and the subscripts w and e refer to water and ethanol, respectively. As the two reactions are of the same kinetic order, this equation predicts that $[ROH]/[ROEt] = k_w p_w / k_e p_e$ and, hence, that the ratio $[ROH]p_e/[ROEt]p_w$ is a constant, independent of the solvent composition.

Solvolysis of benzyl chloride in ethanol–water at 79·94°.

" % " Ethanol *	$10^5 k$†	[ROH]/([ROH] + [ROEt])	$[ROH]p_e/[ROEt]p_w$ ‡
100	6·7 §	—	—
90	15·8 §	0·141	0·57
80	38·3	0·348	1·12
70	65·8	0·642	3·02
60	103	0·838	7·50
50	179	0·884	9·67

* " x% " ethanol was prepared by mixing the solvents in the proportions x ml. of ethanol to (100 − x) ml. of water.
† Rate coefficients for overall solvolysis in sec.$^{-1}$.
‡ Vapour pressures extrapolated from data at lower temperatures (International Critical Tables, Vol. III, p. 290).
§ Initial values of decreasing rate coefficients.

The figures in the last column of the Table show clearly that the requirements of the Olson–Halford equation are not met by the present reactions. Unimolecular solvolysis could be responsible for this observation (though for *tert.*-butyl chloride the corresponding increase of $[ROH]p_e/[ROEt]p_w$ is much less [3]) but, even in " 50% " ethanol, the solvent most favourable to the operation of this mechanism, not more than a small fraction of the total hydrolysis and ethanolysis can proceed without covalent participation by the solvent (see Part I). Admittedly, the Olson–Halford equation neglects the activity coefficients (f_w* and f_e*) of the transition states.[4] Strictly, $[ROH]p_e f_w^*/[ROEt]p_w f_e^*$, and not $[ROH]p_e/[ROEt]p_w$, should be constant, but the transition states for bimolecular hydrolysis and ethanolysis are structurally similar so that we would not expect f_w^*/f_e^* to differ much from unity, or to vary appreciably with changing solvent composition.[2] It does not, therefore, seem likely that neglect of these activity coefficients accounts for the large variations now observed.

At this stage it is necessary to comment briefly on the reaction mechanism. The transition state in the reaction of a solvent molecule, S, with RCl can be regarded as the resonance hybrid of the valence-bond structures (I), (II), and (III) :

$$S\ \ R{-}Cl\ (I);\ \ {}^{+}S{-}R\ \ Cl^{-}\ (II);\ \ S\ \ R^{+}\ Cl^{-}\ (III)$$

In Part I it was concluded that the reaction of benzyl chloride with " 50% " ethanol occurs either *via* two transition states (one for hydrolysis and one for ethanolysis) in which structure (III) is more important than (II), or *via* a whole series of transition states which differ in the contributions of these structures. The effect of solvent changes on the rate suggested that (III) participates to a much smaller extent when no water is present. This is only to be expected since in this structure the electric charges are less dispersed than in (II); it should therefore be more heavily solvated [5] and, hence, be stabilised more than (II) by an increase in the ionising power of the medium. As a result it seems reasonable to consider that (III) becomes progressively more important in the transition state (or

[4] Crunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846; Gold, *Trans. Faraday Soc.*, 1948, **44**, 506.
[5] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, p. 346.

states) for hydrolysis, or ethanolysis, as the solvent is made more aqueous. It is consistent with this view that the solvolysis of benzyl chloride is accelerated less by the addition of small amounts of water to ethanol than the solvolysis of *n*-butyl bromide [where structure (III) makes only a small contribution], and more by the addition of larger amounts.*

The results in the Table show that the proportion of hydrolysis becomes increasingly greater than predicted by the Olson–Halford equation as the water content of the solvent is raised. As this also leads to an increasing participation of (III) in the structure of the transition states, our results can be explained if it is assumed that the greater the importance of (III), the later the stage in the activation process at which covalent bonding with the solvent begins.† Covalent attachment occurs from within the immediate vicinity of the reacting halide where the better solvating agent, water, is present in a larger proportion than in the bulk of the solvent if some partial ionisation has already taken place. Under these conditions water has a better chance of forming a bond than is indicated by its thermodynamic activity in the solvent, and it is this quantity which appears in the kinetic term for hydrolysis in Olson and Halford's rate equation. Such an effect will become progressively more important as we move towards the more aqueous solvents. This interpretation implies that deviations from the Olson–Halford equation are least in the present reactions when the water content is low. Support for this assumption comes from the results for *n*-butyl bromide which are consistent with the view that this equation is valid when the contribution of (III) to the structure of the transition state is small.

The similar but very much smaller increase of $[ROH]p_s/[ROEt]p_w$ in the ethanolysis-hydrolysis of *tert.*-butyl chloride suggests that large variations in this ratio may be characteristic of considerable changes in the transition-state structure with changing solvent composition. If this is the case, a significant participation by both (II) and (III) in solvolytic reactions could be recognised by this method.

Experimental

The experimental techniques were similar to those described in Part I, reaction rates and product proportions being determined from initially *ca.* 0·04M-solutions.

Constant integrated first-order rate coefficients were obtained in all solvents except ethanol and " 90% " ethanol, where these coefficients decreased as the reaction proceeded. This type of behaviour has been noted before and probably results from combination between the liberated acid and the solvent [7]—the reactions were followed by the development of acidity. For these solvents, initial rate coefficients were obtained by graphical extrapolation.

The reaction products after complete solvolysis (*i.e.*, after more than ten " half-lives " had elapsed) were analysed for benzyl alcohol in the following manner, in duplicate or triplicate. Water was added to the solution till it contained equal volumes of ethanol and water. 25 ml. of this mixture were treated with 1 ml. of ammonia (*d* 0·88) to remove excess of acid, and extracted with 10 ml. of light petroleum (b. p. 40—60°). The extract was washed four times with 10 ml. portions of water and cooled to −80°; at this temperature benzyl alcohol was precipitated while benzyl ether remained in solution. The supernatant liquid was decanted off and a stream of air passed at reduced pressure over the residue as it warmed to room temperature, till constant weight was reached; no material was lost as spray provided that the capillary was fine enough. This method gave the amount of benzyl alcohol reproducible to within 1% of the total products, and independent of the presence of up to 0·04 mole of benzyl ether and hydrochloric acid per l. of reaction mixture.

The amount of benzyl ether was found by difference from the initial concentration of the benzyl chloride.

* This is readily demonstrated by interpolating our rate data to the solvent compositions used in the study of *n*-butyl bromide.[8]

† A similar assumption has recently been made in a different context by Hyne and Robertson.[6]

[6] Hyne and Robertson, *Canad. J. Chem.*, 1956, **34**, 863.
[7] Vernon, *J.*, 1954, 4462.

Most experiments were carried out at 79·94°, but the products for reaction with " 50% " ethanol were also examined at 50·60°; here 82·2% of the total reaction resulted in hydrolysis. Comparison with the data at the higher temperature (see Table) then shows that the activation energy for hydrolysis in this solvent is about 3 kcal. mole^{-1} greater than for ethanolysis, provided that each of these processes takes place *via* a single transition state.

One of us (P. R. R.) is indebted to the North Riding of Yorkshire Education Committee for financial support.

THE UNIVERSITY SCIENCE LABORATORIES,
SOUTH ROAD, DURHAM.

[*Received, May 23rd,* 1957.]

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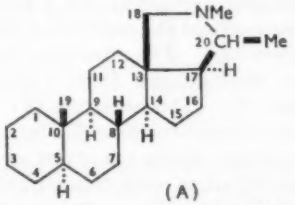
995. *The Constitution of Conessine. Part X.* Oxidation of Conessine and Pyrolysis of Some Oxidation Products.†*

By R. D. HAWORTH and M. MICHAEL.

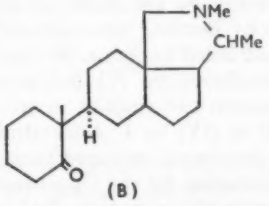
The oxidation of conessine and its derivatives has been examined, and evidence favouring structures (II) and (VII) for " α-oxyconessine " and dioxyconessine respectively have been obtained. Oxidation and pyrolytic experiments along lines similar to those employed in steroid degradation have resulted in the preparation from conessine of derivatives in which (*a*) ring B is ruptured, (*b*) ring B is converted into a five-membered ring, and (*c*) rings A and B are removed leaving the C, D, and E rings of the alkaloid as a basic fragment (XXV) which may be approached by synthesis.

Nomenclature: As a result of consultations with the Editor the following method is adopted for the nomenclature of the conessine derivatives described in this communication.

The trivial name " conanine " is introduced for structure (A) and the assumption is made that conanine retains the stereochemistry of the alkaloid; the α-configuration assigned at position 5 is arbitrary as the alkaloid contains a 5 : 6-double bond. On this



(A)



(B)

basis conessine (I) and dioxyconessine (VII) would become 3β-dimethylaminocon-5-enine and 5 : 6-dihydroxy-3β-dimethylaminoconanine respectively. Application of the steroid rules (*J.*, 1951, 3526), using the *seco* and nor prefixes to indicate reductive bond rupture and ring contraction respectively, leads to 5-oxo-5 : 6-*seco*con-3-enin-6-oic acid, B-norcona-3 : 5-dienine, and 5-oxo-5 : 6-*seco*-B-norconanin-6-oic acid for (IX; R = H), (X), and (XXII; R = H) respectively.

Compounds (XIX) and (XXI) are regarded as hydroxymethylene and carbonyl derivatives of the parent structure (B) and, although it is unlikely that the steroid rules were intended to be used in such a complex way, they would lead to 5-oxo-5 : 8-*seco*-B-bisnorconanine for the parent (B) from which structures (XIX) and (XXI) become 4 : 8-hydroxymethylene- and 4 : 8-carbonyl-5-oxo-5 : 8-*seco*-B-bisnorconanine respectively.

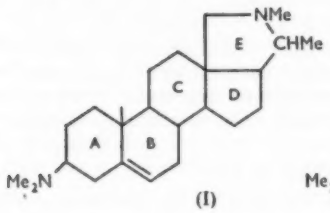
* Part IX, *J.*, 1956, 3749.

† In Part VIII (*J.*, 1955, 986) the $[\alpha]_D$ of 3α-acetamidocholest-5-ene is given as −53°, in reasonable agreement with Bannard and McKay's (*Canad. J. Chem.*, 1955, **33**, 1166) value of −59°, but not with the figures of −30° and −32° given by Shoppee and his collaborators (*J.*, 1955, 694; 1956, 1054). To support a criticism of Bannard and McKay's product, however, Shoppee, Evans, Richards, and Summers (*J.*, 1956, 1649) misquote us as having given in Part VIII the value $[\alpha]_D$ −31°.

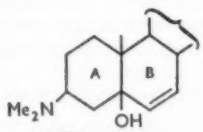
For the nomenclature of the tricyclic ring (XXIV) we propose to use the system employed by Sir Robert Robinson (*J.*, 1952, 1224) in which des-A-cholestane is used for cholestane stripped of the four methylene groups of ring A but retaining the rest of the original asymmetry. Thus (XXIV; R = Me) and (XXIV; R = H) become des-AB-con-8-enine, and de-*N*-methyl-des-AB-con-8-enine respectively.

For some of the products recorded below, configurations cannot be completely assigned. Bonds have therefore been denoted by " ordinary " lines rather than in accordance with the steroid conventions; names, however, are derived from conanine without stereochemical modifications.

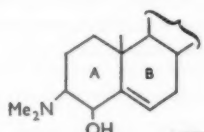
In order to obtain additional constitutional information the behaviour of the steroidal alkaloid conessine (I) towards oxidising agents has been examined. The action of ozone is complex and results in the formation of formaldehyde and water-soluble amorphous products.[1] Oxidation of conessine with selenium dioxide in water yielded Bertho's α-oxyconessine,[1] which probably possesses the 3β-dimethylamino-5-hydroxycon-6-enine structure



(I)

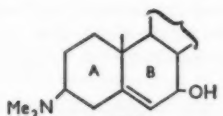


(II)

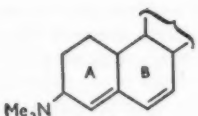


(III)

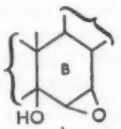
(II) in preference to either of the expected structures (III) or (IV). During attempted oxidation of this compound it was discovered that when treated with hydrogen peroxide in acid solution it readily gave 3β-dimethylaminocona-4 : 6-diene (V), which had been obtained previously by the action of phosphorus oxychloride on a benzene solution of α-oxyconessine by Bertho [2] who however characterised the anhydro-derivative (V) as the dihydriodide but failed to obtain the crystalline base. The ultraviolet absorption spectra of the anhydro-derivative (V) indicated a trisubstituted diene with the conjugation distributed between two rings as in structure (V). This structure (V) could arise from structures (III) or (IV) by 1 : 4-dehydration or from structure (II) by 1 : 2-dehydration, and the latter structure is preferred because we were unable to convert α-oxyconessine into a ketone by oxidation by the Oppenauer procedure or with cold chromic acid. Such a structure (II) probably arises from the isomer (IV) by allylic rearrangement similar to that involved in the conversion of cholest-5-ene-3β : 4β-diol into cholest-4-ene-3β : 6β-diol.[3]



(IV)



(V)



(VI)

Besides yielding the anhydro-derivative (V) the peroxide oxidation of 3β-dimethylamino-5-hydroxycon-6-enine (II) also gave a compound, $C_{24}H_{40}O_2N_2$, m. p. 225—226° (decomp.), which is possibly one of the diastereoisomeric forms of the epoxide (VI); and a second, isomeric epoxide, m. p. 163—164°, was obtained by oxidising 3β-dimethylamino-5-hydroxycon-6-enine with cold chromic acid. Attempts to convert the epoxides into triols were

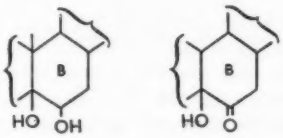
[1] Bertho, *Annalen*, 1947, **557**, 220.
[2] *Idem*, *ibid.*, 1951, **573**, 210.
[3] Rosenheim and Starling, *J.*, 1937, 377; Butenandt and Hausmann, *Ber.*, 1937, **70**, 1154.

unsuccessful and the oxidation of 3β-dimethylamino-5-hydroxycon-6-enine to such epoxides must be regarded as only provisional, as stable epoxides have rarely been isolated by direct oxidation of ethylenes except in the cases of tetrasubstituted derivatives.[4] The isolation of the epoxide, m. p. 163—164°, together with other unidentified products by oxidation of 3β-dimethylamino-5-hydroxycon-6-enine with hot chromic acid is noteworthy in this connection.

The oxidation of conessine with selenium dioxide has been examined with dioxan, pyridine, and " methyl cellosovle " (2-methoxyethanol) as solvent. Another isomeric base, $C_{24}H_{40}O_2N_2$, characterised as a crystalline picrate, and a base, $C_{24}H_{38}O_2N_2$, m. p. 240°, were isolated, but in small yields which prevented thorough investigation.

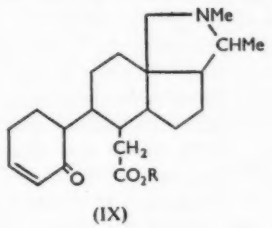
The conversion into 5-acetoxy-3β-dimethylaminocon-6-enine does not involve anionotropic change, as hydrolysis leads to the recovery of 3β-dimethylamino-5-hydroxycon-6-enine. The acetyl derivative was not attacked by iodic acid, but osmium tetroxide gave a product which after hydrolysis yielded still another isomer, $C_{20}H_{40}O_2N_2$, m. p. 240°, of unknown constitution. With potassium permanganate in acetone 5-acetoxy-3β-dimethylaminocon-6-enine gave a poor yield of an oily base which gave a crystalline monomethiodide, indicating that the basicity of one tertiary amino-group has been destroyed either by oxidation of an *N*-methyl to an *N*-formyl group or by oxidation of an $\rangle N\cdot CH_2\cdot$ to an $\rangle N\cdot CO\cdot$ group.

Some properties bearing on the constitution of dioxyconessine (3β-dimethylamino-5 : 6-dihydroxyconanine) were described in Part IV of this series,[5] and evidence in favour of structure (VII) has now been obtained by oxidation with cold chromic acid to 3β-dimethylamino-5-hydroxy-6-oxoconanine (VIII). Although it failed to yield hydroxyl or ketonic derivatives, when heated with formic acid 3β-dimethylamino-5-hydroxy-6-oxoconanine



(VII)

(VIII)

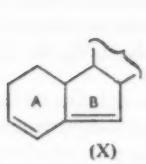


(IX)

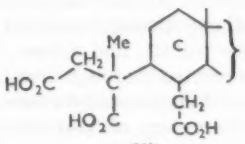
(VIII) gave a mixture of an isomer and another base produced by elimination of dimethylamine. The infrared spectrum of the product (VIII) indicated the presence of a hydroxyl group (3382 cm.$^{-1}$) and a six-membered ring ketone (1698 cm.$^{-1}$). It is also satisfactory that the *OO*-diacetyl derivative of 3β-dimethylamino-5 : 6-dihydroxyconanine, previously described by Giemsa and Halberkann [6] as a varnish, has now been obtained as a crystalline hydrate. Oxidative fission of ring B of 3β-dimethylamino-5 : 6-dihydroxyconanine (VII) was effected with hot chromic acid. This gave dimethylamine and a water-soluble amino-acid mixture from which 5-oxo-5 : 6-*seco*con-3-enin-6-oic acid (IX; R = H) was isolated, and the αβ-unsaturated ketonic structure was supported by the ultraviolet absorption spectra of the acid and its ethyl ester (IX; R = Et). Ring (B) of the alkaloid having been ruptured, it became of interest to determine appropriate conditions for the additional removal of ring (A), and the elegant methods used by Cornforth, Hunter, and Popják [7] in the degradation of cholesterol stimulated the remaining approaches described in this communication. Pyrolysis of the acid (IX; R = H) gave a basic mixture from which the

[4] Petrow, *J.*, 1939, 998; Ruzicka and Bossard, *Helv. Chim. Acta*, 1937, **20**, 244; Petrow and Starling, *J.*, 1940, 60.
[5] Haworth, McKenna, and Whitfield, *J.*, 1953, 1102.
[6] Giemsa and Halberkann, *Arch. Pharm.*, 1918, **256**, 201.
[7] Cornforth, Hunter, and Popják, *Biochem. J.*, 1953, **54**, 590.

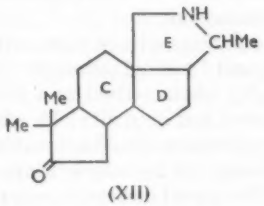
main fraction, isolated by chromatography, was an oil yielding a crystalline methiodide. The ultraviolet spectrum of the oily base was consistent with the trisubstituted heteroannular diene structure of B-norcona-3 : 5-dienine (X). When the amino-acid mixture containing 5-oxo-5 : 6-*seco*con-3-enin-6-oic acid (IX; R = H) was pyrolysed, a small



(X)



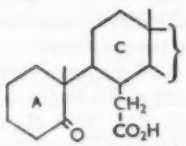
(XI)



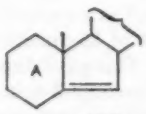
(XII)

amount of a crystalline base, $C_{17}H_{27}ON$, was isolated. Its infrared spectrum indicated the presence of an imino-group (3436 cm.$^{-1}$) and a five-membered ring ketone (1738 cm.$^{-1}$), and the presence of these groups was confirmed by the formation of a nitrosamine and a semicarbazone respectively. Structure (XII), arising from the undetected amino-tricarboxylic acid (XI), is provisionally suggested for the ketonic base, $C_{17}H_{27}ON$.

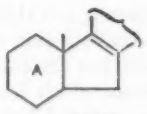
Hydrogenation of the diene (X) could be interrupted at the dihydro-stage, and the product was an oil, yielding a crystalline methiodide. This new oily base lacked the characteristic diene absorption, but residual unsaturation was shown by the ready liberation of iodine from iodic acid as in the conversion of conessine into dioxyconessine. However, as crystalline oxidation products were not obtained either from this reaction with iodic acid or from the action of permanganate in acetone, it was not possible to determine the constitution of the dihydro-product or even to establish its homogeneity. The preparation of a dihydro-derivative of (X) was, however, achieved in another way. Reduction of the amino-acid mixture obtained by oxidation of dioxyconessine with hot chromic acid yielded a mixture, presumably containing 5-oxo-5 : 6-*seco*conanin-6-oic acid (XIII), which on pyrolysis lost water and carbon dioxide and gave the crystalline unsaturated base B-norcon-5-enine (XIV) which was dimorphous and yielded a crystalline methiodide. The hydrochloride, prepared with ethereal hydrogen chloride, was also crystalline, but it was converted by warming with dilute hydrochloric acid into an isomeric hydrochloride which gave a new unsaturated base. This isomerism is possibly due to double-bond migration leading to B-norcon-8(9)-enine (XV) which would account for (*a*) the ready liberation of iodine shown with iodic acid and (*b*) the resistance shown by the new base to reduction by hydrogen in presence of a platinic oxide catalyst.



(XIII)



(XIV)

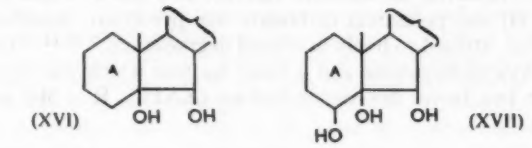


(XV)

An examination has also been made of the behaviour of B-norcon-5-enine (XIV) towards a number of oxidising agents. Iodic acid, hydrogen peroxide in acid solution, and chromic acid gave intractable gums, and ozonolysis followed by catalytic reduction of the ozonide gave non-basic amorphous material, probably by oxidation of the *N*-methyl group or the α-methylene group as well as attack at the double bond (see analogous behaviour in the annotonine series [8]). However, pyrolysis of the crude ozonolysis product resulted in the

[8] Betts and MacLean, *Canad. J. Chem.*, 1957, **35**, 211.

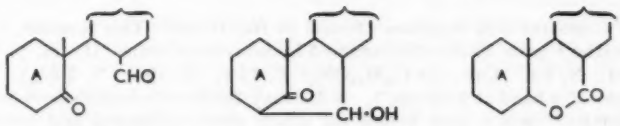
formation of 2-methyl*cyclo*hexanone, and a higher-boiling non-basic material, which unfortunately rapidly darkened and could not be investigated further. Potassium periodate, recently advocated as a reagent for double bonds,[9] reacted with the base (XIV)



(XVI) (XVII)

to give poor yields of 5 : 6-dihydroxy-B-norconanine (XVI), and a triol, possibly 4 : 5 : 6-trihydroxy-B-norconanine (XVII). It has been suggested [9,10] that periodate reacts *via* the epoxide and, since epoxides on fission give *trans*-diols,[11] a 5 : 6-*trans*-diol structure is favoured for (XVI); this diol certainly differs from the isomeric 5 : 6-*cis*-diol described below. The structure assigned to the triol (XVII) is based on the assumption that this compound arises from the diol (XVI) by dehydration and subsequent hydroxylation; if this is so, and if the hydroxylation proceeds by way of an epoxide which is cleaved to give two axial hydroxyl groups, then the triol (XVII) is a 4β : 5α : 6ξ-triol.

The 5 : 6-*cis*-diol (XVI), mentioned above, was obtained by the action of osmium tetroxide on B-norcon-5-enine (XIV). Reaction of this *cis*-diol with periodate gave, not the expected 5 : 6-dioxo-5 : 6-*seco*-B-norconanine (XVIII), but the isomeric 4 : 8-hydroxymethylene-5-oxo-5 : 8-*seco*-B-bisnorconanine (XIX) which formed a monosemicarbazone and whose infrared spectrum showed the presence of a hydroxyl group (3345 cm.$^{-1}$) and a six-membered ring ketone (1700 cm.$^{-1}$). Bredt's rule provides an explanation of the failure to convert the aldol (XIX) into an αβ-unsaturated ketone, and several cases of analogous aldol formation have been reported by Julia *et al.*[12] and by Prelog and Osgan.[13] When the aldol base (XIX) was treated with alkali in an attempt to induce a reversed aldolisation to 5 : 6-dioxo-5 : 6-*seco*-B-norconanine (XVIII), it was converted into 5-hydroxy-5 : 6-*seco*-B-norconanin-6-oic 5 : 6-lactone (XX), which is probably formed by dismut-

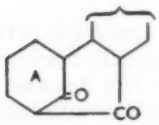


(XVIII) (XIX) (XX)

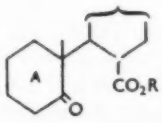
ation of the keto-aldehyde (XVIII) as observed by Cornforth, Gore, and Popják [14] in an analogous case. Direct pyrolysis of 4 : 8-hydroxymethylene-5-oxo-5 : 8-*seco*-B-bisnorconanine (XIX) gave 2-methyl*cyclo*hexanone and a small basic fraction from which a crystalline picrate was isolated, but in quantities insufficient for characterisation. Careful oxidation of the aldol (XIX) with chromic acid in cold acetic acid gave the β-diketone, 4 : 8-carbonyl-5-oxo-5 : 8-*seco*-B-bisnorconanine (XXI), which on alkaline hydrolysis underwent cleavage to 5-oxo-5 : 6-*seco*-B-norconanin-6-oic acid (XXII; R = H), which was characterised as its crystalline methyl ester. The direction of alkaline cleavage of the β-diketone (XXI) was established by direct oxidation of 5 : 6-*cis*-dihydroxy-B-norconanine

[9] Chatterjee and Majumdar, *Analyt. Chem.*, 1956, **28**, 878.
[10] Graber, Snoddy, Arnold, and Wendler, *J. Org. Chem.*, 1956, **21**, 1518.
[11] Winstein and Henderson in "Heterocyclic Compounds," Ed. Elderfield, Wiley, New York, 1950, Vol. I, p. 27.
[12] Julia, Eschenmoser, Heusser, and Tarkoy, *Helv. Chim. Acta*, 1953, **36**, 1888.
[13] Prelog and Osgan, *ibid.*, 1952, **35**, 981.
[14] Cornforth, Gore, and Popják, *Biochem. J.*, 1957, **65**, 94.

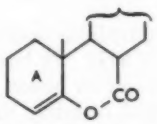
(XVI) in small yield to the same amino-acid (XXII; R = H). Pyrolysis of methyl 5-oxo-5 : 6-*seco*-B-norconanin-6-oate (XXII; R = Me) yielded the enol-lactone, 5-hydroxy-5 : 6-*seco*-B-norcon-4-enin-6-oic 5 : 6-lactone (XXIII), which was characterised as the methiodide. When, however, an intimate mixture of 5-oxo-5 : 6-*seco*-B-norconanin-6-oic acid (XXII; R = H) and potassium carbonate was pyrolysed, decarboxylation and the reverse Michael fission, utilised so freely in steroid degradations,[7,12,14,15] took place with the formation of 2-methyl*cyclo*hexanone and a basic fraction which was separated by chromatography into the two bases, des-AB-con-8-enine (XXIV; R = Me) and de-*N*-methyl-



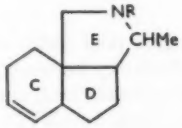
(XXI)



(XXII)



(XXIII)



(XXIV)

des-AB-con-8-enine (XXIV; R = H). The tertiary base (XXIV; R = Me) was an oil which gave a crystalline picrate; the secondary base (XXIV; R = H) was also an oil but gave an oily nitrosamine, showing a positive Liebermann test, and yielded a crystalline picrate. Catalytic reduction of des-AB-con-8-enine (XXIV; R = Me) gave a dihydro-derivative, des-AB-conanine, as an oil from which a crystalline picrate was prepared.

At this stage the quantities of the bases (XXIV; R = Me and H) were insufficient for further characterisation or for further degradation, and consequently experiments have been commenced which aim at the synthesis of these rather inaccessible compounds.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°. Ultraviolet absorption spectra were measured for 95% ethanol solutions, and infrared absorption spectra with potassium bromide discs.

Oxidation of Conessine with Selenium Dioxide in Hot Water.—This reaction, carried out as described by Bertho,[1] gave 3β-dimethylamino-5-hydroxycon-6-enine (II), m. p. 158° (Found: C, 77·4; H, 11·1; N, 7·8. Calc. for $C_{24}H_{40}ON_2$: C, 77·4; H, 10·8; N, 7·5%). The infrared spectrum had *inter al.* a band at 3382 cm.$^{-1}$. 5-Acetoxy-3β-dimethylaminocon-6-enine, prepared according to Bertho,[16] was a pale yellow oil which slowly solidified and crystallised from aqueous acetone in colourless needles, m. p. 128° (Found: C, 75·2; H, 10·5; N, 6·9. Calc. for $C_{26}H_{42}O_2N_2$: C, 75·3; H, 10·2; N, 6·8%). Hydrolysis with N-methanolic potassium hydroxide gave 3β-dimethylamino-5-hydroxycon-6-enine, m. p. 158°. 3β-Dimethylamino-5-hydroxycon-6-enine was recovered after being refluxed with aluminium *iso*propoxide or *tert.*-butoxide in a mixture of toluene and *cyclo*hexanone.

Oxidation of 3β-Dimethylamino-5-hydroxycon-6-enine (II) with Cold Chromic Acid.—To a solution of 3β-dimethylamino-5-hydroxycon-6-enine (250 mg.) in acetic acid (20 ml.) was added a solution of chromium trioxide (90 mg.) in water (1·5 ml.) and acetic acid (4·5 ml.). After 87 hr. the solution was made alkaline by addition of sodium hydroxide, and the *epoxide*, isolated with ether, was a gum (230 mg.) which slowly solidified under light petroleum and separated from acetone in needles, m. p. 163—164° (Found: C, 74·0; H, 10·5; N, 7·1. $C_{24}H_{40}O_2N_2$ requires C, 74·2; H, 10·4; N, 7·2%), which were unaffected by boiling dilute sulphuric acid or by potassium hydroxide in boiling aqueous ethanol or aqueous dioxan.

Action of Hydrogen Peroxide on 3β-Dimethylamino-5-hydroxycon-6-enine.—3β-Dimethylamino-5-hydroxycon-6-enine (100 mg.), 2N-sulphuric acid (2·5 ml.), and 30% hydrogen peroxide

[15] Achtermann, *Z. physiol. Chem.*, 1934, **225**, 141; Laucht, *ibid.*, 1935, **237**, 236; Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579; 1954, **76**, 1390; Rinikier, Arigoni, and Jeger, *Helv. Chim. Acta*, 1954, **37**, 547.

[16] Bertho, *Annalen*, 1950, **569**, 1.

(0·15 ml.) were heated on the water-bath for 3 hr. Excess of peroxide was destroyed with sulphur dioxide, and the solution basified and extracted three times with ether. Removal of the solvent gave a gummy *epoxide* (85 mg.) which crystallised from acetone in colourless prisms (21 mg.), m. p. 225—226° (Found: C, 74·1; H, 10·4; N, 7·0. $C_{24}H_{40}O_2N_2$ requires C, 74·2; H, 10·4; N, 7·2%). The acetone mother-liquors were evaporated, and the residue was taken up in light petroleum and chromatographed on alumina (2 g.). Elution with light petroleum–ether (1 : 1) gave an oil which slowly solidified and was crystallised from aqueous acetone. 3β-*Dimethylaminocona*-4 : 6-*dienine* (V) (28 mg.) was obtained as colourless needles, m. p. 116° (Found: C, 81·7; H, 11·0; N, 8·0. $C_{24}H_{36}N_2$ requires C, 81·4; H, 10·7; N, 7·9%) undepressed on admixture with the product, m. p. 116°, of the action of phosphorus oxychloride on 3β-dimethylamino-5-hydroxycon-6-enine.[2] The diene had ultraviolet absorption max. at 2320, 2390, 2470 Å (infl.) (log ε 4·3, 4·35, 4·2).

Oxidation of Conessine with Selenium Dioxide in Dioxan.—Conessine (500 mg.) in pure dioxan (10 ml.) was refluxed with selenium dioxide (780 mg.) for 3 hr. The solvent was removed, water was added to the residue, and the selenium removed at a centrifuge. Basification of the aqueous layer and extraction with ether gave a gum (180 mg.), which was taken up in benzene and chromatographed on alumina (5 g.). Elution with more benzene gave crystals (60 mg.), m. p. 175—180°, recrystallising from *cyclo*hexane in colourless needles, m. p. 179—180°, which gave inconsistent analytical results but yielded a *picrate* separating from acetone in yellow needles, m. p. 110° (Found: C, 58·1; H, 7·2. $C_{24}H_{40}O_2N_2,C_6H_3O_7N_3$ requires C, 58·3; H, 7·0%).

Elution with chloroform yielded a *base* (27 mg.), m. p. 235—238°, which separated from benzene–light petroleum in colourless prisms, m. p. 240° (Found: C, 74·5; H, 9·9; N, 7·2. $C_{24}H_{38}O_2N_2$ requires C, 74·5; H, 9·9; N, 7·3%).

Similar results were obtained in pyridine or " methyl cellosolve."

Oxidation of 5-*Acetoxy*-3β-*dimethylaminocon*-6-*enine with Osmium Tetroxide.*—This acetate (1 g.) and osmium tetroxide (1 g.) in dry ether (100 ml.) were allowed to react at room temperature for 16 days. After evaporation of solvent the residue was shaken overnight with mannitol (5 g.) and N-potassium hydroxide (20 ml.). The alkaline solution was extracted three times with ether, the extracts were combined, and the solvent was removed. The residue (690 mg.) was divided into two parts and treated as follows:

(*a*) The gum (303 mg.) was refluxed with N-methanolic potassium hydroxide (10 ml.) for 1 hr. The methanol was removed, water added, and the product, isolated with ether, chromatographed on alumina (8 g.). Elution with ether gave 3β-dimethylamino-5-hydroxycon-6-enine (II) (82 mg.), m. p. and mixed m. p. 158°, and elution with ether–chloroform (1 : 1) yielded an oily *base* (110 mg.) which slowly crystallised and had m. p. 230—236°. Recrystallisation from *cyclo*hexane gave colourless needles, m. p. 239—241° (Found: C, 74·0; H, 10·0. $C_{24}H_{40}O_2N_2$ requires C, 74·2; H, 10·4%).

(*b*) The gum (276 mg.) was treated on the steam-bath with N-sulphuric acid (10 ml.) for 2 hr. After basification, the product was isolated with ether and chromatographed on alumina (8 g.), giving 3β-dimethylaminocona-4 : 6-dienine (V) (90 mg.), m. p. 116°, and a substance (38 mg.) which separated from *cyclo*hexane in colourless needles, m. p. 180°, which was not analysed.

Oxidation of 5-*Acetoxy*-3β-*dimethylaminocon*-6-*enine with Potassium Permanganate.*—A solution of potassium permanganate (420 mg.) in acetone (70 ml.) was added with shaking to a solution of 5-acetoxy-3β-dimethylaminocon-6-enine (410 mg.) in acetone (70 ml.). After 12 hr. at room temperature, the manganese dioxide was collected and washed with acetone, and the combined washings and filtrate were evaporated. The residue was taken up in ether, washed with dilute aqueous sodium hydroxide, and dried and the solvent removed. The residual gum (337 mg.) was chromatographed in ether–light petroleum (1 : 1) on alumina (9 g.), and separated into 5-acetoxy-3β-dimethylaminocon-6-enine (210 mg.), m. p. 128°, and an oil which gave a *monomethiodide* as colourless plates (from acetone), m. p. 234—235° (Found: C, 54·7; H, 7·8; N, 4·85. $C_{27}H_{43}O_2N_2I,H_2O$ requires C, 55·1; H, 7·7; N, 4·8%).

Dioxyconessine (3β-*Dimethylamino*-5 : 6-*dihydroxyconanine*).—The method of preparation described by Bertho [1] was more convenient than Warnecke's method [17] for the preparation of large quantities. The infrared spectrum had, *inter al.*, bands at 3382 and 3143 cm.$^{-1}$.

5 : 6-*Diacetoxy*-3β-*dimethylaminoconanine*.—3β-Dimethylamino-5 : 6-dihydroxyconanine (200

[17] Warnecke, *Arch. Pharm.*, 1888, **226**, 248.

mg.), pyridine (4 ml.), and acetic anhydride (1 ml.) were heated for 2 hr. on the steam-bath. Evaporation under reduced pressure and addition of water (1 ml.) gave an oil which crystallised during two days in a vacuum-desiccator over sulphuric acid. Recrystallisation from acetone gave 5 : 6-*diacetoxy*-3β-*dimethylaminoconanine monoacetate* as colourless needles, m. p. 194—196° (decomp.) (preheated bath) (Found: C, 67·8; H, 9·3; N, 5·2. $C_{28}H_{46}O_4N_2,CH_3{\cdot}CO_2H$ requires C, 67·4; H, 9·4; N, 5·2%). 5 : 6-Diacetoxy-3β-dimethylaminoconanine was prepared by dissolving this salt in dilute hydrochloric acid and basifying the solution with dilute sodium hydroxide; the base was collected, washed with a little water, dried, and crystallised from aqueous methanol; the *hydrate* separated as small needles (Found: C, 68·2; H, 10·3. $C_{28}H_{46}O_4N_2,H_2O$ requires C, 68·2; H, 9·9%) which when heated in a m. p. tube lost water and collapsed to a resin, m. p. 130—135°. The *methiodide*, prepared in acetone, separated from methanol in stout prisms, m. p. 296° (decomp.) (Found: C, 46·5; H, 7·2; N, 3·8. $C_{28}H_{46}O_4N_2,2CH_3I,H_2O$ requires C, 46·4; H, 7·0; N, 3·6%). Attempted partial hydrolysis of 5 : 6-diacetoxy-3β-dimethylaminoconanine hydrate was unsuccessful.

Oxidation of Dioxyconessine with Cold Chromic Acid.—A solution of chromium trioxide (200 mg.) in water (2·5 ml.) and acetic acid (7·5 ml.) was added to dioxyconessine (585 mg.) in acetic acid (40 ml.). After 72 hr. at room temperature, excess of oxidising agent was destroyed by addition of methanol (5 ml.), and the basified solution was continuously extracted with chloroform for 12 hr. Removal of the chloroform gave 3β-*dimethylamino*-5-*hydroxy*-6-*oxoconanine* (VIII) which separated from ethanol in stout needles, m. p. 281—282° (Found: C, 73·8, 74·2; H, 10·5, 10·6; N, 7·2, 7·2. $C_{24}H_{40}O_2N_2$ requires C, 74·2; H, 10·4; N, 7·2%), which sublimed at 180°/10 mm. The infrared spectrum had, *inter al.*, bands at 3382 and 1698 cm.$^{-1}$.

Attempts to prepare a semicarbazone, an acetyl derivative, or an enol-acetate led to recovery of 3β-dimethylamino-5-hydroxy-6-oxoconanine which did not react with selenium dioxide, *N*-bromosuccinimide, benzaldehyde, potassium periodate, or phosphorus oxychloride. When 3β-dimethylamino-5-hydroxy-6-oxoconanine was refluxed for 117 hr. with 98—100% formic acid it was converted into an *isomer* which separated from acetone in long needles, m. p. 193—195° (Found: C, 73·8; H, 10·5; N, 7·5. $C_{24}H_{40}O_2N_2$ requires C, 74·2; H, 10·4; N, 7·2%). The acetone mother-liquors after evaporation, dissolution in ether, adsorption on alumina, and elution with ether-chloroform (1 : 1) yielded a *substance* which crystallised from acetone–light petroleum in prisms, m. p. 204—205° (decomp.) (Found: C, 76·9; H, 9·9; N, 4·1. $C_{22}H_{33}O_2N$ requires C, 76·9; H, 9·7; N, 4·1%).

Oxidation of Dioxyconessine with Warm Chromic Acid.—Chromium trioxide (5·5 g.) in water (200 ml.) was slowly added to a solution of dioxyconessine (11 g.) in 10% sulphuric acid (100 ml.) on the steam-bath. After 1 hr. the cooled mixture was basified with barium hydroxide, the precipitated chromium hydroxide and barium sulphate were removed on a centrifuge and washed with warm water, the combined washings and aqueous liquors were heated to the b. p., and the volatile bases passed into aqueous picric acid. Dimethylamine picrate was isolated; it had m. p. 157—158° after crystallisation from alcohol. Carbon dioxide passed through the non-volatile aqueous solution precipitated barium carbonate which was removed. The filtrate was evaporated to dryness under reduced pressure. The amino-acid mixture remained as a friable mass (8·8 g.) which crystallised, with difficulty, from acetone containing a small amount of water and gave 5-*oxo*-5 : 6-seco*con*-3-*enin*-6-*oic acid sesquihydrate* (cf. IX; R = H) as colourless prisms, m. p 193—196° (decomp.) (Found: C, 68·7; H, 9·2; N, 4·0. $C_{22}H_{33}O_3N,1\frac{1}{2}H_2O$ requires C, 68·3; H, 9·4; N, 3·6%), $\lambda_{max.}$ 2270 Å (log ε 4·0). The water of crystallisation was retained at 60°/0·01 mm. for 12 hr. The amino-acid mixture (6·5 g.), heated for 6 hr. with saturated ethanolic hydrogen chloride (150 ml.), gave a brown gum (6·3 g.), which was chromatographed in light petroleum on alumina (120 g.). A light petroleum–benzene (1 : 1) eluate (3·3 g.) yielded *ethyl* 5-*oxo*-5 : 6-seco*con*-3-*enin*-6-*oate* (IX; R = Et) as a pale yellow oil, b. p. 195° (bath)/0·03 mm. (Found: C, 74·2; H, 9·9; N, 3·6. $C_{24}H_{37}O_3N$ requires C, 74·4; H, 9·6; N, 5·6%), $\lambda_{max.}$ 2270 Å (log ε 4·0).

Further elution of the alumina with ether yielded a *substance* which separated from light petroleum in colourless needles (120 mg.), m. p. 103—104° (Found: C, 75·3, 75·2; H, 9·8, 10·0; N, 3·0, 3·3. $C_{26}H_{41}O_3N$ requires C, 75·2; H, 9·9; N, 3·4%), which was not identified.

Pyrolysis of 5-*Oxo*-5 : 6-seco*con*-3-*enin*-6-*oic Acid* (IX; R = H).—The amino-acid mixture (6·2 g.) was mixed with dry potassium carbonate (15 g.) and iron filings (6 g.) and heated with a free flame. Water and carbon dioxide were eliminated and a yellow oil distilled. The combined distillates from two such operations were mixed with the ether extract from the

non-volatile material. The non-basic fraction (380 mg.) remained in the ether after washing with dilute hydrochloric acid, and the basic material (4·82 g.) was recovered by basification, isolated with ether, and chromatographed in light petroleum–benzene (1 : 1) on alumina (125 g.). Elution with the same solvent gave B-norcona-3 : 5-diene (X) as an oil (2·20 g.) which with methyl iodide in warm benzene gave the *methiodide*, crystallising from acetone in colourless plates, m. p. 265—267° (Found: C, 60·0; H, 7·9; N, 2·8. $C_{22}H_{34}NI$ requires C, 60·1; H, 7·8; N, 3·2%). The oil (X) had $\lambda_{max.}$ 2400 (log ε 4·1) and 2450 Å (log ε 4·1), but did not react with maleic anhydride. Further elution of the alumina with benzene removed a *ketone* as an oil which slowly crystallised; the crystals (190 mg.) were sublimed at 80°/0·01 mm. and recrystallised from aqueous acetone in colourless needles, m. p. 98—99° (Found: C, 77·9, 77·9; H, 10·2, 10·4; N, 5·4. $C_{17}H_{27}ON$ requires C, 78·1; H, 10·4; N, 5·4%), having infrared bands at, *inter al.*, 3436 and 1738 cm.$^{-1}$, giving a positive Liebermann test and a *semicarbazone* which separated from aqueous acetone in colourless needles, m. p. 162—163° (Found: N, 15·8. $C_{18}H_{30}ON_4,2H_2O$ requires N, 15·8%).

Hydrogenation of B-*Norcona*-3 : 5-*diene* (X).—The diene (196 mg.) in ethanol (10 ml.) was hydrogenated at room temperature in the presence of 5% palladium–charcoal (390 mg.). The uptake of hydrogen was slow and the saturation of one double bond (uptake: 18·9 ml.) occupied 12 hr. The dihydro-compound (180 mg.) was an oil with no characteristic ultraviolet maximum, and readily liberated iodine from iodic acid. The *methiodide*, prepared in benzene, crystallised from acetone–ether in colourless plates, m. p. 257—258° (Found: C, 59·8, 60·0; H, 8·5, 8·3; N, 2·8, 2·9; I, 29·1. $C_{22}H_{36}NI$ requires C, 59·85; H, 8·2; N, 3·2; I, 28·8%).

Pyrolysis of 5-*Oxo*-5 : 6-*seco*-*conanin*-6-*oic acid* (XIII).—The amino-acid mixture (15 g.) [containing (IX; R = H)] in ethanol (100 ml.) was shaken with hydrogen in presence of 10% palladium–charcoal (4 g.) for 15 hr.; hydrogen uptake was then complete. Filtration and evaporation of the solvent gave 5-oxo-5 : 6-*seco*conanin-6-oic acid (XIII) as a light brown friable mass, the alcoholic solution of which showed no characteristic ultraviolet absorption. A mixture of the crude reduction product (6·6 g.) and dry potassium carbonate (3·3 g.) was heated, water and carbon dioxide being evolved. The residue was distilled under reduced pressure, the products from two such operations were combined, and the basic fraction (6·2 g.) was isolated as described for an analogous case above. A light petroleum solution of the basic fraction was chromatographed on alumina (180 g.) and eluted first with the same solvent to give a colourless oil (*A*) (3·37 g.) and then with ether–light petroleum (1 : 1) to yield a pale yellow oil (*B*) (1·65 g.). The oil (*A*) slowly solidified and crystallisation from acetone gave B-*norcon*-5-*enine* (XIV) as stout colourless needles, m. p. 78—79° (Found: C, 84·1; H, 11·4; N, 4·6. $C_{21}H_{33}N$ requires C, 84·2; H, 11·1; N, 4·7%). The acetone mother-liquors gradually deposited a dimorphous *form* as colourless rectangular prisms, m. p. 78—79° (Found: C, 84·1; H, 11·2; N, 5·2%), and when inoculated with this prismatic form the oil (*B*) rapidly solidified, and in subsequent reactions the dimorphous forms were indistinguishable. The base liberated iodine from iodic acid, but showed no characteristic ultraviolet absorption. The *hydrochloride*, prepared with ethereal hydrogen chloride, separated from methanol–acetone in colourless needles, m. p. 268° (decomp.) (Found: C, 74·7; H, 10·0; N, 4·2; Cl, 11·0. $C_{21}H_{34}NCl$ requires C, 75·1; H, 10·2; N, 4·2; Cl, 10·6%). The *picrate*, prepared from aqueous solution, crystallised from aqueous acetone in yellow needles, m. p. 100° (Found: C, 59·7; H, 7·2; N, 10·2. $C_{21}H_{33}N,C_6H_3O_7N_3,H_2O$ requires C, 59·3; H, 7·0; N, 10·1%). The *methiodide*, prepared in benzene, crystallised from acetone–benzene in colourless plates, m. p. 261—262° (Found: C, 60·0; H, 7·9; N, 2·9. $C_{21}H_{33}N,CH_3I$ requires C, 59·5; H, 8·2; N, 3·2%). The *dihydro-derivative* (B-*norconanine*), prepared in acetic acid solution by using Adams platinic oxide, crystallised from acetone in large prisms, m. p. 67—68° (Found: C, 83·6; H, 11·5; N, 4·2. $C_{21}H_{35}N$ requires C, 83·6; H, 11·7; N, 4·6%), which did not liberate iodine from iodic acid.

Action of Dilute Hydrochloric Acid on B-*Norcon*-5-*enine* (XIV).—An ethereal solution of the base (XIV) was treated with 2N-hydrochloric acid, and the crystalline hydrochloride which separated from the aqueous phase was collected. The crystals became gummy overnight in a vacuum-desiccator and, when the gum was warmed on the steam-bath with dilute hydrochloric acid, the solution became cloudy and after 40 min. set to a crystalline mass. These crystals were collected and dried; recrystallisation from methanol–acetone gave the isomeric *hydrochloride* in colourless needles, m. p. 274° (decomp.) (Found: C, 73·1; H, 10·3; N, 4·4; Cl, 9·8. $C_{21}H_{33}N,HCl,\frac{1}{2}H_2O$ requires C, 73·1; H, 10·2; N, 4·1; Cl, 10·3%). The isomeric base [B-*norcon*-8(9)-*enine*] (XV) was obtained as stout needles, m. p. 114·5—115° (Found: C, 84·0;

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H, 11·3; N, 5·2. $C_{21}H_{33}N$ requires C, 84·2; H, 11·1; N, 4·7%), unchanged after attempted reduction in acetic acid in presence of Adams platinic oxide.

Action of Periodic Acid on B-*Norcon-5-enine* (XIV).—The base (XIV) (128 mg.) was added to a solution of potassium periodate (1 g.) in N-sulphuric acid (40 ml.). After 20 hr. at room temperature, the solution was cooled to 0° and basified with sodium hydroxide. The product, isolated with ether, was a gum (120 mg.) which gave 4 : 5 : 6-*trihydroxy*-B-*norconanine* (XVII) as colourless prisms (38 mg.), m. p. 234—235° (decomp.) (Found: C, 71·9; H, 10·1; N, 4·5. $C_{21}H_{35}O_3N$ requires C, 72·2; H, 10·1; N, 4·0%), on crystallisation from methanol–acetone. The mother-liquors were evaporated; the residue solidified under light petroleum at 0° and after crystallisation from *cyclo*hexane yielded 5 : 6-trans-*dihydroxy*-B-*norconanine* (XVI) as needles (35 mg.), m. p. 168—169° (Found: C, 75·8; H, 10·6; N, 4·5. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6; N, 4·2%).

Action of Osmium Tetroxide on B-*Norcon-5-enine* (XIV).—A solution of the base (XIV) (1 g.) and osmium tetroxide (1 g.) in ether (80 ml.) was refluxed for 120 hr., and the precipitated osmic ester was collected and washed with ether. Evaporation of the filtrate gave unchanged base (XIV) (333 mg.), m. p. 78—79°. After the precipitated osmic ester had been shaken with mannitol (5 g.) and N-potassium hydroxide (30 ml.) for 12 hr., water (52 ml.) was added and the solution was extracted four times with chloroform. The extract was washed with water, the solvent removed, and the residual dark brown gum (650 mg.) chromatographed in ether on alumina (20 g.). Elution with ether yielded a dark brown gum (450 mg.) which crystallised on trituration with light petroleum, and after two crystallisations from *cyclo*hexane 5 : 6-cis-*dihydroxy*-B-*norconanine* was obtained as needles (265 mg.), m. p. 184—185° (Found: C, 75·4; H, 10·5; N, 4·5. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6; N, 4·2%).

Action of Periodic Acid on 5 : 6-cis-*Dihydroxy*-B-*norconanine* (XVI).—After 40 hr. at room temperature a solution of the *cis*-diol (100 mg.), potassium periodate (100 mg.), and N-sulphuric acid (5 ml.) was cooled to 0°, then basified with dilute sodium hydroxide; 4 : 8-*hydroxymethylene*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XIX) (95 mg.), isolated with ether, separated from *cyclo*hexane in needles, m. p. 179—180° (Found: C, 76·4; H, 10·1; N, 4·5. $C_{21}H_{33}O_2N$ requires C, 76·1; H, 10·0; N, 4·2%). The infrared spectrum had, *inter al.*, bands at 1700 and 3345 $cm.^{-1}$. The *semicarbazone*, prepared in methanol, crystallised from acetone in colourless plates, m. p. 220—221° (Found: N, 14·4. $C_{22}H_{36}O_2N_4$ requires N, 14·4%).

Action of Alkali on 4 : 8-*Hydroxymethylene*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XIX).—The aldol (XIX) (50 mg.) in methanol was heated for 90 min. in a nitrogen atomosphere with potassium hydroxide (160 mg.) in water (1 ml.). Water (5 ml.) was added and the solution neutralised to pH 7 with 2N-sulphuric acid. The precipitate (29 mg.) was collected and crystallised twice from light petroleum; 5-*hydroxy*-5 : 6-seco-B-*norconanin*-6-*oic* 5 : 6-*lactone* (XX) separated in colourless prisms, m. p. 131—132° (Found: C, 76·0; H, 10·0; N, 3·8. $C_{21}H_{33}O_2N$ requires C, 76·1; H, 10·0; N, 4·2%).

Pyrolysis of 4 : 8-*Hydroxymethylene*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XIX).—The aldol (XIX) (328 mg.) was mixed with potassium carbonate (164 mg.) and pyrolysed with a free flame. The product, treated as described previously for an analogous case, gave non-basic (42 mg.) and basic fractions (109 mg.); the former was identified as 2-methyl*cyclo*hexanone by the preparation of the 2 : 4-dinitrophenylhydrazone, m. p. 134—135°. The basic material, which showed no characteristic maximum in the ultraviolet spectrum, was chromatographed in light petroleum on alumina (3 g.). Elution with the same solvent gave an oil (16 mg.), which yielded a picrate, m. p. 226° (decomp.) after crystallisation from acetone; the quantities were insufficient for analysis or further examination.

Oxidation of 4 : 8-*Hydroxymethylene*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XIX).—A solution of the aldol (XIX) (100 mg.) and chromium trioxide (31 mg.) in acetic acid (9·5 ml.) and water (0·5 ml.) was kept at room temperature for 50 hr., and excess of oxidising agent was then removed by warm alcohol (5 ml.). Most of the acetic acid was removed *in vacuo*, the solution was basified with dilute sodium hydroxide solution, and 4 : 8-*carbonyl*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XXI) isolated with ether; it crystallised from aqueous acetone in colourless needles, m. p. 121—122° (Found: C, 76·0; H, 9·4; N, 4·5. $C_{21}H_{31}O_2N$ requires C, 76·5; H, 9·5; N, 4·3%).

Action of Alkali on 4 : 8-*Carbonyl*-5-*oxo*-5 : 8-seco-B-*bisnorconanine* (XXI).—The diketone (XXI) (100 mg.), barium hydroxide (5 ml. of saturated solution), and water (5 ml.) were heated for 2 hr. on the steam-bath. After removal of unchanged diketone (3 mg.) with ether, the

aqueous liquors were saturated with carbon dioxide, and the barium carbonate was removed. Evaporation of the filtrate gave crude 5-oxo-5 : 6-*seco*-B-norconanin-6-oic acid (XXII; R = H) which was esterified with ethereal diazomethane; the *methyl ester* (XXII; R = Me) separated from light petroleum in stout prisms, m. p. 131—132° (Found: C, 72·9; H, 9·8; N, 3·9. $C_{22}H_{35}O_3N$ requires C, 73·1; H, 9·8; N, 3·9%). The ester methiodide crystallised from acetone in colourless prisms, m. p. 290° (decomp.).

Preparation of Methyl 5-Oxo-5 : 6-seco-B-*norconanin-6-oate* (XXII; R = Me) *from 5* : 6-cis-*Dihydroxy*-B-*norconanine* (XVI).—A solution of the *cis*-diol (XVI) (100 mg.) in 10% sulphuric acid (1 ml.) was warmed on the steam-bath with chromium trioxide (40 mg.) in water (2 ml.) for 30 min. Isolation of the amino-acid fraction as described for dioxyconessine gave a gum (52 mg.) which, methylated in ether with diazomethane, gave methyl 5-oxo-5 : 6-*seco*-B-norconanin-6-oate (XXII; R = Me), m. p. 131—132°, identical with that obtained from the diketone (XXI).

Pyrolysis of Methyl 5-Oxo-5 : 6-seco-B-*norconanin-6-oate* (XXII; R = Me).—The ester (50 mg.) was heated at 335—340° in an evacuated sealed tube, and the product chromatographed in light petroleum on alumina (1 g.). Elution with light petroleum–ether (1 : 1) gave 5-hydroxy-5 : 6-*seco*-B-norcon-4-enin-6-oic 5 : 6-lactone (XXIII) as a pale yellow oil (25 mg.) which did not crystallise on inoculation with starting material. The *methiodide* separated from methanol–acetone in colourless prisms, m. p. 299—300° (decomp.) (Found: C, 55·05; H, 7·4; N, 3·1. $C_{21}H_{31}O_2N,CH_3I,\frac{1}{2}H_2O$ requires C, 55·0; H, 7·3; N, 2·9%).

Pyrolysis of 5-Oxo-5 : 6-seco-B-*norconanin-6-oic Acid* (XXII; R = H).—The amino-acid (200 mg.) was mixed with dry potassium carbonate (100 mg.) and heated with a free flame until distillation ceased. The distillates from four such operations were combined and separated into non-basic (160 mg.) and basic (380 mg.) fractions. 2-Methyl*cyclo*hexanone, isolated as the 2 : 4-dinitrophenylhydrazone, m. p. 133—134°, was obtained from the non-basic fraction. The basic material was treated with light petroleum, filtered from insoluble material (120 mg.), and chromatographed on alumina (9 g.). Elution with light petroleum gave a colourless odourless oil (*A*; 50 mg.) and light petroleum–ether (1 : 1) removed a pale yellow oil (*B*; 132 mg.) with a powerful odour.

Fraction *A* gave a picrate which, after three crystallisations from ethanol, gave the *picrate of des*-AB-*con*-8-*enine* (XXIV; R = Me) as straw-coloured needles, m. p. 178—179° (decomp.) (Found: C, 54·0; H, 5·7; N, 13·4. $C_{19}H_{24}O_7N_4$ requires C, 54·3; H, 5·75; N, 13·3%). The free base, isolated from the pure picrate (18 mg.) on treatment with lithium hydroxide, was reduced with Adams platinum oxide and hydrogen in acetic acid. The picrate of the des-AB-conanine was obtained as yellow needles, m. p. 153—154°, from aqueous acetone but there was insufficient for analysis.

Fraction *B* was converted into the picrate which separated from a little acetone in dark yellow needles. Two crystallisations from acetone–carbon tetrachloride gave *de*-N-*methyldes*-AB-*con*-8-*enine picrate* (cf. XXIV; R = H) as yellow needles, m. p. 236—238° (decomp.) (evacuated tube; bath preheated to 230°) (Found: C, 53·3; H, 5·3; N, 14·0. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·5; N, 13·8%). The picrate (9 mg.) was decomposed with lithium hydroxide, and de-*N*-methyldes-AB-con-8-enine (XXIV; R = H) extracted into ether. It had a very powerful odour and gave a positive Liebermann nitroso-test.

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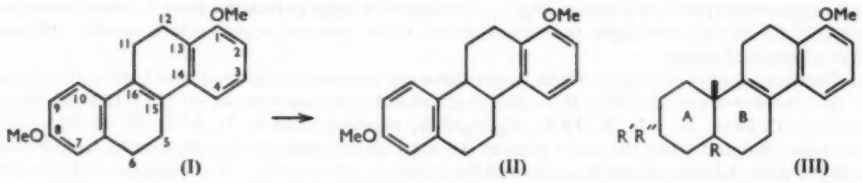
996. *Absence of Stereochemical Selectivity in the Reduction of* 5 : 6 : 11 : 12-*Tetrahydro- to* 5 : 6 : 11 : 12 : 15 : 16-*Hexahydro*-1 : 8-*dimethoxychrysene by Dissolving Metals.*

By P. A. Robins and James Walker.

Reduction of the 15 : 16-double bond in 5 : 6 : 11 : 12-tetrahydro-1 : 8-dimethoxychrysene (I) with (*a*) sodium and butan-1-ol, or (*b*) sodium, lithium, or potassium and an alcohol in liquid ammonia, gave mixtures containing approximately equal proportions of *cis*- and *trans*-5 : 6 : 11 : 12 : 15 : 16-hexahydro-1 : 8-dimethoxychrysene (II).

Birch and Smith [1] have recently described the reduction of 5 : 6 : 11 : 12-tetrahydro-1 : 8-dimethoxychrysene (I) by sodium in boiling butan-1-ol to 5 : 6 : 11 : 12 : 15 : 16-hexahydro-1 : 8-dimethoxychrysene (II), an intermediate in the preparation of some D-homo-18 : 19-bisnor-steroids, and claimed that the *trans*-form of (II) is the major constituent of the mixture of *cis*- and *trans*-isomers formed. At the time of their communication we had almost completed an extensive investigation * of this reduction, our starting material being obtained by an alternative route.[2] We now report our results, which indicate that this reduction appears to be non-stereoselective, although appropriate experimental conditions [1] may permit the isolation of more of the *trans*-form of (II) than of the *cis*-stereoisomer. There is also no evidence to show that the similar reduction of the 2 : 8-dimethoxy-isomer of (I) takes place stereoselectively.[3] In contrast to these observ-



(I) (II) (III)

ations, Johnson and his collaborators [4,5] have reported that reduction with lithium and alcohol in liquid ammonia of a series of substances (III) takes place with varying degrees of stereoselectivity, depending upon the nature of the substituents (R, R', R'') and the *trans*- or *cis*-arrangement of rings A and B, to give the products of *trans*- [4] or *cis*-reduction [5] of the styrene double bond.

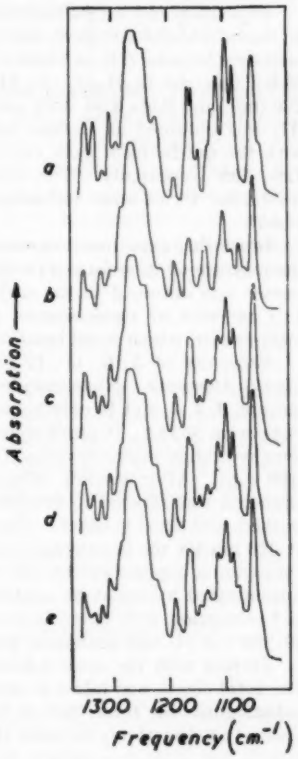
We have already described [2] the catalytic reduction of the compound (I) to give the *cis*-stereoisomer (II). Reduction of the substance (I) with sodium in boiling butan-1-ol gave a mixture, from which the *trans*-stereoisomer of (II) was isolated in relatively poor yield by repeated crystallisation, whereas Birch and Smith,[1] more fortunate than ourselves in finding satisfactory conditions for crystallisation, obtained a fraction rich in *trans*-isomer directly from the reaction mixture in 40% yield, but further crystallisation, or chromatography, was necessary to obtain a completely pure product. The infrared absorption spectra of the two pure stereoisomers of (II) were recorded (Figure; *a*, *b*), and

* The essence of the present paper was communicated, and the figure was shown as a slide, at a meeting of the Society on October 18th, 1956, during the discussion of the paper by Professor Birch and Dr. Smith.

[1] Birch and Smith, *J.*, 1956, 4909.
[2] Robins and Walker, *J.*, 1956, 3249, 3260.
[3] Birch and Smith, *J.*, 1951, 1882.
[4] Johnson, *J. Amer. Chem. Soc.*, 1956, **78**, 6278; Johnson, Rogier, Szmuszkovicz, Hadler, Ackerman, Bhattacharyya, Bloom, Stalman, Clement, Bannister, and Wynberg, *ibid.*, p. 6289.
[5] Johnson, Ackerman, Eastham, and DeWalt, *ibid.*, p. 6302.

the spectrum of a 1 : 1 mixture of the two (Figure; *c*) was compared with that of the crude product from another reduction of (I) with sodium and butan-1-ol; the last pair of spectra were indistinguishable (Figure; *c*, *e*) over the region in which substantial differences were discernible in the spectra of the pure *cis*- and *trans*-stereoisomers of (II).

In view of the apparent absence of stereoselectivity in the above reduction a series of experiments employing alkali-metal–alcohol–liquid ammonia systems was carried out. In these cases also the reduction of the tetrahydro- (I) to the hexahydro-compound (II) was non-stereoselective (cf. Figure; *d*). Although with a large excess of sodium and propan-2-ol in liquid ammonia reduction did not proceed beyond the introduction of two hydrogen atoms to give compound (II), reduction readily proceeded further with lithium or potassium and ethanol in liquid ammonia, even when low temperatures and small



Infrared spectrum of: (*a*) cis-5 : 6 : 11 : 12 : 15 : 16-*hexahydro*-1 : 8-*dimethoxychrysene*; (*b*) trans-5 : 6 : 11 : 12 : 15 : 16-*hexahydro*-1 : 8-*dimethoxychrysene*; (*c*) *a* 1 : 1 *mixture of* cis- *and* trans-5 : 6 : 11 : 12 : 15 : 16-*hexahydro*-1 : 8-*dimethoxychrysene*; (*d*) 5 : 6 : 11 : 12 : 15 : 16-*hexahydro*-1 : 8-*dimethoxychrysene from the reduction of* 5 : 6 : 11 : 12-*tetrahydro*-1 : 8-*dimethoxychrysene with sodium and propan*-2-*ol in liquid ammonia*; *and* (*e*) 5 : 6 : 11 : 12 : 15 : 16-*hexahydro*-1 : 8-*dimethoxychrysene from the reduction of* 5 : 6 : 11 : 12-*tetrahydro*-1 : 8-*dimethoxychrysene with sodium and butan*-1-*ol*.

excesses of metal were employed, to give crude products giving some ketonic material on acid hydrolysis (cf. Birch and Smith [1]). The hexahydro-compound (II) in every case appeared to be a 1 : 1 mixture of *cis*- and *trans*-stereoisomers. The tetrahydro-compound (I) was not reduced by lithium aluminium hydride in boiling tetrahydrofuran or by Goodman's lithium aluminium hydride–Carbitol reagent,[6] the starting material being recovered in each case.

It thus appears from our results that reduction by dissolving metals of the 15 : 16-double bond in the almost planar molecule (I) is non-stereoselective, and that the stereoselective reductions observed by Johnson and his collaborators [4,5] are controlled to a considerable extent by steric and polar [5] factors.

[6] Goodman, *J.*, 1951, 2209.

Experimental

Reduction of 5 : 6 : 11 : 12-*Tetrahydro*-1 : 8-*dimethoxychrysene* (I) *with Sodium and Butan*-1-*ol*.—Sodium (0·24 g., 30 atom-equiv.) was added to a solution of the tetrahydrodimethoxychrysene (I) (0·1 g.) in boiling butan-1-ol. When all the sodium had dissolved the butanol was removed by steam-distillation, and the product was recovered by extraction with ether. The solid residue obtained on evaporation of the dried ethereal solution showed strong ultraviolet absorption of the anisole type at 279 mμ (log ε 3·66), while absorption at 330 mμ indicated that less than 2% of the starting material remained unchanged. The infrared absorption spectrum (Figure; *e*) (carbon tetrachloride solution) was indistinguishable from that of a 1 : 1 mixture of the pure *cis*- and *trans*-stereoisomers of 5 : 6 : 11 : 12 : 15 : 16-hexahydro-1 : 8-dimethoxychrysene (II).

Repetition on a larger scale, followed by repeated recrystallisation of the crude product from methanol–chloroform, gave, with poor recovery, *trans*-5 : 6 : 11 : 12 : 15 : 16-hexahydro-1 : 8-dimethoxychrysene (II) as needles, micro-m. p. 130·5—131·5° (Found: C, 81·2; H, 7·5; MeO, 20·6. Calc. for $C_{20}H_{22}O_2$: C, 81·6; H, 7·5; 2MeO, 20·7%), $\lambda_{max.}$ (in hexane) 274 (infl.), 279, 286 (infl.) mμ (log ε 3·50, 3·55, and 3·31 respectively). On another occasion the *trans*-compound (II) was obtained as leaflets, micro-m. p. 133—137°, which on recrystallisation and seeding with the needle form gave the latter. The leaflets on melting and cooling then remelted at 129—130° repeatedly. The infrared spectra in carbon tetrachloride solution of the two crystalline forms were indistinguishable. Birch and Smith [1] record needles, m. p. 133·5—134·5°.

In another experiment chromatography on alumina was employed in an attempt to separate the mixture of stereoisomers obtained in the reduction. Some concentration of the *cis*-stereoisomer was obtained in the earlier fractions, but the m. p. fell on recrystallisation until the 1 : 1 mixture of stereoisomers resulted. Later fractions contained a concentration of the *trans*-isomer, which could be obtained in poor yield only after several crystallisations.

Reduction of 5 : 6 : 11 : 12-*Tetrahydro*-1 : 8-*dimethoxychrysene* (I) *by Alkali-metal–Alcohol–Liquid Ammonia*.—Experiments were carried out using 4, 10, and 12·5 atomic proportions of sodium, 3, 4, 5, and 10 of lithium, and 10 of potassium, and the following experiment is typical. Potassium (0·14 g., 10 atom-equiv.) was added in several pieces with stirring to a solution of the tetrahydrodimethoxychrysene (I) (0·1 g.) in dry tetrahydrofuran (20 c.c.) and liquid ammonia (100 c.c.). After 10 min. ethanol (5 c.c.) was added to discharge the blue colour and the ammonia was allowed to evaporate. Water was then added and the product was recovered, washed, and dried in ether. The crude sticky product showed 89% of the expected absorption at 279 mμ for the hexahydro-compound (II), and gave with acid alcoholic 2 : 4-dinitrophenylhydrazine a copious precipitate of an orange derivative. Hydrolysis in ethanol (25 c.c.) with concentrated hydrochloric acid (3 c.c.) under reflux for ½ hr., followed by dilution with water and extraction with ether, gave an oil. This was dissolved in benzene–light petroleum (b. p. 40—60°) (1 : 4) and allowed to percolate down a column of activated alumina (10 g.).

Elution with the same solvent mixture left the ketonic material adsorbed on the column. The total eluate was taken to dryness, and the infrared absorption spectrum of the residue was indistinguishable from that of the 1 : 1 mixture of *cis*- and *trans*-5 : 6 : 11 : 12 : 15 : 16-hexahydro-1 : 8-dimethoxychrysene (II).

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997. *A Potentiometric and Polarographic Study of Copper–Catechol Complexes.*

By C. F. Timberlake.

Complex formation between catechol (H_2A) and cupric ions (Cu^{2+}) in aqueous solution at 25° has been studied by potentiometric titration and the stability constants of complexes CuA and CuA_2^{2-} have been determined. The polarographic behaviour of both unbuffered and buffered aqueous systems of copper and catechol at 25° has also been studied. In solutions containing phosphate buffers with pH 7—8, CuA_2^{2-} was reversibly reduced at the dropping mercury electrode and its stability constant, calculated from polarographic measurements, agreed with that obtained potentiometrically. From the results we estimated concentrations of Cu^{2+}, CuA, and CuA_2^{2-} in some copper–catechol systems.

Although complexes of copper and catechol were isolated and described by Weinland and Walter[1] in 1923, it is only recently that a quantitative potentiometric study of their formation has been reported by Näsanen and Markkanen.[2] Our work, started independently and before Näsanen and Markkanen's publication, confirmed their findings: in addition, the determination of the second dissociation constant of catechol has enabled the stability constants of these complexes to be evaluated. Further, the polarographic behaviour of both unbuffered and buffered copper–catechol systems has confirmed the potentiometric results. The interaction of cupric ions with phenols, mainly of the catechol type, in fruit juice buffered with organic acids has been described.[3,4]

Results and Discussion

Potentiometric Measurements.—Graphs relating the pH of solution to the ratio of concentration of added base to concentration of copper (m_b/m_{Cu}), obtained on titration of catechol solutions containing cupric chloride with sodium hydroxide, showed inflections at values of (m_b/m_{Cu}) of 2 and 4, corresponding to the neutralisation of 2 and 4 hydrogen ions per atom of copper present (Figure). The reactions can be represented by eqns. (1) and (2) where catechol is regarded as a dibasic acid H_2A.

$$Cu^{2+} + H_2A \rightleftharpoons CuA + 2H^+ \quad (1) \; ; \qquad CuA + H_2A \rightleftharpoons CuA_2^{2-} + 2H^+ \quad (2)$$

The concentration equilibrium constants for these reactions are

$$K_1^1 = [CuA]\{H^+\}^2/[Cu^{2+}][H_2A] \quad (3) \; ; \quad \text{and } K_2^1 = [CuA_2^{2-}]\{H^+\}^2/[CuA][H_2A] \quad (4)$$

The activity equilibrium constants are

$$K_1 = [CuA]\{H^+\}^2/f_2[Cu^{2+}][H_2A] \quad (5) \; ; \quad \text{and } K_2 = f_2[CuA_2^{2-}]\{H^+\}^2/[CuA][H_2A] \quad (6)$$

where f_2 represents the ionic activity coefficient of ions of charge ± 2, and the square brackets and braces enclosing the ionic species represent concentrations and activities respectively.

Calculation of K_1. K_1 was calculated from consideration of the ionic species present and (i) the electroneutrality equation, (ii) the total concentration of catechol ($[A_o]$), and (iii) the total concentration of copper ($[Cu_o]$). Over the pH range studied $[HA^-]$, $[A^{2-}]$, and $[OH^-]$ were negligible, so that

$$[H_2A] = [A_o] - [Na^+]/2 - [H^+]/2 \text{ and } [CuA] = [Na^+]/2 + [H^+]/2$$

[1] Weinland and Walter, *Z. anorg. Chem.*, 1923, **126**, 145.
[2] Näsanen and Markkanen, *Suomen Kem.*, 1956, **29**, 119.
[3] Kieser, Pollard, and Timberlake, *J. Sci. Food Agric.*, 1957, **8**, 151.
[4] Timberlake, *ibid.*, p. 159.

pH was defined as equal to $-\log_{10}\{H^+\}$ and $pK = -\log_{10} K$. The hydrogen-ion concentrations were sufficiently low to permit $\{H^+\}$ to be used for $[H^+]$. Ionic strengths were all calculated from $I = 0{\cdot}5\sum m_i z_i^2$ where m is the molar concentration of ions of type i and valency z_i, and ion-activity coefficients were evaluated from the Davies [5] equation, *viz.*, $\log f_i = -0{\cdot}5\ z_i^2\{\sqrt{I}/(1+\sqrt{I}) - 0{\cdot}2\ I\}$.

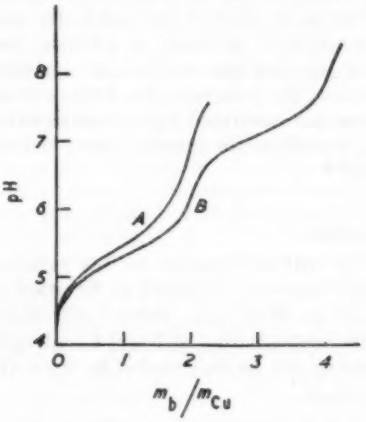
Values of pK_1 calculated from points on the buffer range of the graph obtained by titration of a solution of catechol and cupric chloride in the ratio 1 : 1 are given in

TABLE 1. *Measurement of* K_1.

Titration of 20 ml. of 0·005M-catechol and 4 ml. of 0·025M-$CuCl_2,2H_2O$ with 0·050N-NaOH.)

NaOH (ml.)...	0·20	0·40	0·80	1·24	1·77	2·00	2·27	2·76	3·27	3·51	3·70
pH	4·709	4·886	5·090	5·249	5·422	5·498	5·589	5·782	6·052	6·224	6·422
pK_1[1]	8·269	8·286	8·287	8·281	8·278	8·271	8·276	8·279	8·278	8·231	8·183
10^2I	12·2	11·9	11·3	10·7	9·9	9·6	9·3	8·6	8·1	7·7	7·2
pK_1	8·075	8·094	8·099	8·098	8·103	8·105	8·104	8·112	8·117	8·072	8·029

Table 1. The relatively constant value obtained (mean 8·10) at pH 5·090—6·052 indicated that CuA was the only complex existing under these conditions. Further pH



Potentiometric titration. *A*, Titration of 20 ml. of 0·005M-catechol and 4 ml. of 0·025M-$CuCl_2,2H_2O$ with 0·050N-NaOH; *B*, Titration of 40 ml. of 0·005M-catechol and 2 ml. of 0·025M-$CuCl_2,2H_2O$ with 0·050N-NaOH.

measurements in solutions containing catechol, cupric chloride, and sodium hydroxide in the ratio 1 : 1 : 1 gave pK_1 values of 8·11 and 8·12. The value of pK_1 was taken as 8·11, in agreement with the previous value [2] of 8·09.

Calculation of K_2. K_2 was calculated from consideration of the ionic species present and (i) the electroneutrality equation, (ii) the total concentration of catechol ($[A_o]$), (iii) the total concentration of copper ($[Cu_o]$), and (iv) the first dissociation constant ${}_cK_1$ of catechol, whence

$$[H_2A] = (2[A_o] - [Na^+] - [H^+] + [OH^-])/(2 + {}_cK_1/[H^+])$$

$$[CuA_2^{2-}] = ([Na^+] + [H^+] - [OH^-] - 2[Cu_o] - {}_cK_1[H_2A]/[H^+])/2$$

At pH values over 7, $[HA^-]$ although small was taken into account. The concentrations of H^+ and OH^- were sufficiently small to permit activities to be used for concentrations.

Constant values of K_2 were obtained from points on the second buffer range of the titration graph of a solution of catechol and copper chloride in ratio 4 : 1 (curve *B*, Figure), indicating that CuA_2^{2-} was the only other complex existing with CuA. pK_2 was 11·76, in close agreement with the value of 11·73 found previously.[2]

[5] Davies, *J.*, 1938, 2093.

The validity of the Davies equation up to ionic strength 0·10 was confirmed for K_1 and K_2 by pH measurements of catechol–cupric chloride–sodium hydroxide solutions to which known amounts of solid potassium nitrate were added. Relative constancy of pK_2 values is shown in the results in Table 2.

TABLE 2. *Effect of ionic strength.*

Additions of solid KNO_3 to 40 ml. of 0·0025M-catechol, 1 ml. of 0·025M-$CuCl_2,2H_2O$, and 3 ml. of 0·025N-NaOH.

10^3I	2·0	11·1	20·3	29·7	47·7	66·0	92·5
pH	7·254	7·201	7·189	7·157	7·131	7·098	7·070
pK_2^1	11·673	11·567	11·543	11·479	11·427	11·361	11·305
pK_2	11·758	11·753	11·783	11·762	11·767	11·743	11·735

Dissociation constants of catechol. The dissociation constants of catechol,

$$ {}_cK_1 = f_1^2[H^+][HA^-]/[H_2A] \quad . \quad . \quad (7); \quad \text{and } {}_cK_2 = f_2[H^+][A^{2-}]/[HA^-] \quad . \quad . \quad (8) $$

were determined by titration of catechol solutions with potassium hydroxide. The concentrations of the ionic species were found from eqns. (9)—(11).

$$ [Na^+] + [H^+] = [HA^-] + 2[A^{2-}] + [OH^-] \quad . \quad . \quad . \quad . \quad . \quad (9) $$

$$ [H_2A] + [HA^-] + [A^{2-}] = [A_0] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10) $$

$$ {}_cK_1 = f_1^2[H^+][HA^-]/[H_2A] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11) $$

Ionic strengths and activity coefficients were obtained by successive approximinations, and pOH was determined from $pK_w - pH$, where $pK_w = 13{\cdot}9966$.[6] Results of a typical titration are shown in Table 3, which includes values of the Bjerrum $\bar{n}$ function and the Speakman [7] parameters X and Y.

TABLE 3. *Dissociation constants of catechol.*

Titration of 40 ml. of 0·01M-catechol with 0·101N-KOH.

KOH (ml.)	pH	$10^3[A_0]$	$10^3[K^+]$	10^3I	$10^3[OH^-]$	$10^3[H_2A]$	$10^3[HA^-]$	$10^3[A^{2-}]$	$\bar{n}$	$10^{21}X$	$10^{13}Y$
1·5	9·207	9·640	3·651	3·66	0·01730	6·006	3·634	—	1·622	69·05	196·1
2·0	9·424	9·526	4·809	4·83	0·02877	4·746	4·780	—	1·533	35·40	100·4
2·5	9·639	9·412	5·940	5·96	0·04753	3·520	5·892	—	1·374	17·36	49·20
3·7	10·352	9·154	8·551	8·63	0·2495	0·927	8·151	0·076	1·170	1·118	2·835
3·9	10·542	9·111	8·973	9·05	0·4055	0·615	8·416	0·080	1·059	0·494	1·177
4·1	10·741	9·072	9·391	9·49	0·6124	0·397	8·576	0·099	1·033	0·207	0·428
4·3	10·908	9·031	9·797	9·93	0·9016	0·266	8·624	0·141	1·014	0·099	0·125
4·5	11·046	8·989	10·21	10·39	1·242	0·198	8·612	0·179	1·002	0·053	0·014
4·7	11·154	8·950	10·62	10·75	1·596	0·153	8·567	0·230	0·991	0·033	−0·044

The mean value of ${}_cK_1$ was $3{\cdot}57 \times 10^{-10}$ ($p_cK_1 = 9{\cdot}45$), in agreement with that found previously.[2] The value of ${}_cK_1{}_cK_2$ was $0{\cdot}052 \times 10^{-21}$, obtained from the intercept of the straight line of slope ${}_cK_1$ according to Speakman's method, and also from ${}_cK_1{}_cK_2 = f_2\{H^+\}^2$ at $\bar{n} = 1$; hence ${}_cK_2 = 1{\cdot}5 \times 10^{-13}$ ($p_cK_2 = 12{\cdot}8$). As far as we know, only one value for ${}_cK_2$ has recently been published [8] ($p_cK_2 = 11{\cdot}23$ at ionic strength 0·06).

Stability constants of CuA *and* CuA_2^{2-}. The stability constants of CuA and CuA_2^{2-}, *viz.*:

$$ K_{s1} = [CuA]/f_2^2[Cu^{2+}][A^{2-}] \quad . \quad (12); \quad \text{and } K_{s2} = [CuA_2^{2-}]/[CuA][A^{2-}] \quad . \quad (13) $$

can be calculated from

$$ K_{s1} = K_1/{}_cK_1{}_cK_2 \quad . \quad . \quad . \quad . \quad (14); \quad \text{and } K_{s2} = K_2/{}_cK_1{}_cK_2 \quad . \quad . \quad . \quad (15) $$

[6] Harned and Hamer, *J. Amer. Chem. Soc.*, 1933, **55**, 2194.
[7] Speakman, *J.*, 1940, 855.
[8] Trujillo, Brito, and Cabrera, *Anales real Soc. españ. Fis. Quim.*, 1956, **52**, *B*, 589.

giving $\log_{10} K_{s1} = 14{\cdot}1$ and $\log_{10} K_{s2} = 10{\cdot}5$. The overall stability constant of the reaction $Cu^{2+} + 2A^{2-} \rightleftharpoons CuA_2^{2-}$ is

$$K_s = [CuA_2^{2-}]/f_2^2[Cu^{2+}][A^{2-}]^2 = K_{s1}K_{s2} \quad . \quad . \quad . \quad . \quad (16)$$

Therefore $\log_{10} K_s = 24{\cdot}6$.

Polarography.—Initially, buffer-free solutions of catechol and cupric ions similar to those studied potentiometrically were investigated in which the distributions of cupric ions and cupric complexes were known from pH measurements. The results are in Table 4.

TABLE 4. *Polarography of unbuffered solutions.*

Additions of NaOH (0·025N) to a solution (5 ml.) of catechol (0·004M), $Cu(NO_3)_2,3H_2O$ (0·001M), KNO_3 (0·05M), and methyl-red (0·0004%).

	Potentiometric titration					
Soln.	NaOH (ml.)	pH	Cu^{2+} (%)	CuA (%)	CuA_2^{2-} (%)	$[Cu^{2+}]$ (10^4M)
A	0	4·60	98	2	—	9·8
B	0·1	5·17	75	25	—	7·3
C	0·2	5·48	50	50	—	4·8
D	0·3	5·76	25	75	—	2·4
E	0·4	6·27	—	100	—	—
F	0·5	6·80	—	75	25	—
G	0·6	7·07	—	50	50	—
H	0·7	—	—	25	75	—

	Polarography				
Soln.	No. of waves	First wave $E_{\frac{1}{2}}$ (uncorr.)	Second wave $E_{\frac{1}{2}}$ (uncorr.)	Relative wave-heights	$[Cu^{2+}]$ from wave-height (10^4M)
A	2	+0·03	−0·27 to −0·28	6·8 : 0·2	9·7—9·9
B	2	+0·03	−0·27 to −0·29	4·6 : 1·0	6·6—7·3
C	2	+0·03	−0·28 to −0·31	2·9 : 1·6	4·0—4·4
D	2	+0·03	−0·30 to −0·32	variable	1·7—3·3
E	2	−0·03	−0·31 to −0·36	1·6 : 2·7	—
F	2	−0·06	−0·35 to −0·36	1·1 : 3·1	—
G	2	−0·08	−0·36	0·1 : 3·5	—
H	1	−0·38	—	—	—

In each solution the wave caused by reduction of cupric ions was well defined, except at low Cu^{2+} concentrations, and represented fairly accurately the bulk concentrations of these ions. The diffusion-controlled nature of this wave was shown by measurements of the diffusion current (i_d) at various heights of the mercury reservoir (h). Constant values of $i_d/\sqrt{h}$ were obtained on polarography of solution *C* (Table 4) at head heights ranging from 25 to 75 cm. (drop times 3·05—9·08 sec.). The other waves in the solutions were ill-defined and bore no relation to the bulk concentrations of CuA and CuA_2^{2-} because of the increase in pH produced at the electrode surface by liberation of A^{2-} ions during discharge of the complexes.

The use of acetate buffers over pH range 5—6 in attempts to maintain constant pH at the electrode surface increased the height of the first wave and shifted the half-wave potential slightly in a negative direction. The wave-height of the second wave was considerably reduced and the half-wave potential became more positive. Apparently at these pH values, acetate had also formed a complex with copper, and the first wave represented the reduction of both cupric ions and the cupric–acetate complex. The absence of any kinetic contribution to the height of this wave was confirmed by the constancy of the ratio $i_d/\sqrt{h}$ at different heights of the mercury reservoir (drop times 3·69—7·53 sec.). The behaviour of phthalate buffer (0·1M, pH 5·8) was similar to that of acetate. Phosphate buffer (0·05M, pH 5·8) similarly interfered and some copper was precipitated.

Buffer solutions should compete with catechol for cupric ions over the pH range described since the values of K_1[1] and K_2[1] indicate that the apparent stabilities of the catechol complexes are low at these pH values. With increasing pH, however, the cupric–catechol complexes become more stable rapidly (the apparent stability of CuA_2^{2-} increases with $[H^+]^{-4}$), and at high pH values no interference by the usual buffer systems

TABLE 5. *Polarographic measurements at high catechol concentration.*

Solutions of catechol (0·781M), cupric nitrate (0·000409M), and methylcellulose (0·0125%) in phosphate–NaOH buffers (0·0469M-KH_2PO_4); $(E_{\frac{1}{2}})_s = +0{\cdot}031$ v.

pH	6·90	7·21	7·48	7·74	8·07	
Slope	0·034	0·032	0·031	0·030	0·032	
$(E_{\frac{1}{2}})_c$ (v)	−0·193	−0·233	−0·261	−0·289	−0·327	
ΔE (v)	−0·224	−0·264	−0·292	−0·320	−0·358	
log K_s	24·6	24·7	24·6	24·5	24·5	Mean 24·6

would be expected. This was confirmed by the polarography of solutions containing cupric nitrate, phosphate buffers of pH range 7—8, a large excess of catechol and methylcellulose as maximum suppressor. Well-defined single waves were obtained at each pH. Reversibility was demonstrated by plotting $\log_{10} i/(i_d - i)$ against potential for each wave. Straight lines were obtained with slopes varying from 0·030 to 0·034 (Table 5), in close agreement with the theoretical slope of 0·0296 at 25° for a reversible two-electron reduction. Half-wave potentials were obtained from the intercepts of the lines on the potential scale.

The concentration of A^{2-}, although low relative to that of copper, may be assumed to be kept constant at the electrode surface, and equal to that in the bulk of the solution, through rapid establishment of equilibrium between the various catechol species, present in large excess. A similar assumption was made in the polarographic investigation of copper in solutions of ethylenediaminetetra-acetic acid.[9] The shift in half-wave potential is then given by

$$\Delta E = (E_{\frac{1}{2}})_c - (E_{\frac{1}{2}})_s = -(\boldsymbol{RT}/n\boldsymbol{F}) \ln (K_s f_c k_s / f_s k_c) - (p\boldsymbol{RT}/n\boldsymbol{F}) \ln [A^{2-}] f_2 \quad . \quad (17)$$

where the subscripts c and s refer to complex and simple cupric ions respectively, k_c and k_s are constants proportional to the square-roots of the diffusion coefficients, n is the number of electrons involved in the reduction process, p is the number of A^{2-} ions associated with each Cu^{2+} ion, and K_s is the stability constant of the complex formed from Cu^{2+} and A^{2-}. Substitution in eqn. (17) from eqns. (7) and (8) gives

$$-\Delta E = (\boldsymbol{RT}/n\boldsymbol{F}) \ln (K_s f_c k_s / f_s k_c) + (p\boldsymbol{RT}/n\boldsymbol{F})(2\mathrm{pH} - \mathrm{p}C K_1 - \mathrm{p}C K_2) + (p\boldsymbol{RT}/n\boldsymbol{F}) \ln [H_2A] \quad . \quad (18)$$

Equation (18) predicts that if $[H_2A]$ is maintained constant and if $n = 2$ and $p = 2$, a plot of $-\Delta E$ against pH will give a straight line of slope 0·118. A linear relation was found between ΔE and pH (Table 5), the slope being 0·112, in sufficient agreement with 0·118 to justify our regarding the complex present in solution as preponderantly CuA_2^{2-}.

$(E_{\frac{1}{2}})_s$ was measured in a solution containing cupric nitrate (0·000409M), methylcellulose (0·0125%), and potassium nitrate (0·0469M). From observation of the relative wave-heights, k_s/k_c was 1·2; the value of log K_s (Table 5) was then calculated from equation (18) and agreed with that found potentiometrically.

The temperature coefficient of the diffusion current measured in the solution of pH 7·21, at 14—55°, varied from 1·6 to 1·8% per degree, *i.e.*, of the order of magnitude associated with a diffusion-controlled electrode process. The diffusion-controlled nature of the electrode reaction was further confirmed by the constancy of the values of $i_d/\sqrt{h}$, measured

[9] Pecsok, *Analyt. Chem.*, 1953, **25**, 561.

in the solution of pH 7·21 at different heights of the mercury reservoir. The results are shown in Table 6, which also includes values of the diffusion-current constant I calculated from the Ilkovič equation. Using the mean value of I (2·55), we calculate the diffusion coefficient (D) of the CuA_2^{2-} ion to be $4{\cdot}41 \times 10^{-6}$ cm.^{2} sec.$^{-1}$.

TABLE 6. *Effect of height of mercury column.*

Solution pH 7·21, Table 5; m and t measured at −0·24 v.

	Height of nercury column		
	30 cm.	60 cm.	80 cm.
h (corr.) (cm.)	28·4	58·4	78·4
m (mg. sec.$^{-1}$)	0·963	1·986	2·689
t (sec.)	7·70	3·76	2·76
i_d (μA)	1·45	2·05	2·35
$i_d/\sqrt{h}$ (corr.)	0·272	0·268	0·266
I	2·59	2·55	2·51

Distribution of Cupric Ions and Complexes.—A knowledge of the stability constants of CuA and CuA_2^{2-} enables the distribution of copper in the forms Cu^{2+}, CuA, and CuA_2^{2-} to be calculated for solutions of known pH containing copper and catechol of known concentrations. In such solutions the three species Cu^{2+}, CuA, and CuA_2^{2-} must exist in the following proportions:

$$Cu^{2+} : CuA : CuA_2^{2-} = 1 : f_2^2K_{s1}[A^{2-}] : f_2^2K_{s1}K_{s2}[A^{2-}]^2 \quad . \quad . \quad (19)$$

where $[A^{2-}]$ is the equilibrium concentration of bivalent catechol anions existing in solution. $[A^{2-}]$ can be evaluated from eqn. (20):

$$f_2^2\alpha K_{s1}K_{s2}[A^{2-}]^3 - f_2^2(X-2)[Cu_o]K_{s1}K_{s2}[A^{2-}]^2 + f_2^2\,\alpha K_{s1}[A^{2-}]^2 - f_2^2(X-1)[Cu_o]K_{s1}[A^{2-}] + \alpha[A^{2-}] = X[Cu_o] \quad . \quad (20)$$

where $$X = [A_o]/[Cu_o]$$

and $$\alpha = (1 + f_2[H^+]/_cK_2 + f_1^2f_2[H^+]^2/_cK_{1c}K_2)$$

Equation (20) is similar to that used for complexes of copper and glycine.[10]

The magnitudes of the stability constants K_{s1} and K_{s2} are such that the three species cannot exist in appreciable quantities at the same time in solution. Cu^{2+} and CuA can exist together, with CuA_2^{2-} negligible, and CuA and CuA_2^{2-} can exist together, with Cu^{2+} negligible. At concentrations of A^{2-} smaller than 10^{-13} only Cu^{2+} and CuA need be considered in the theoretical treatment of the system and at pH values below 6, the first two terms in α are negligible compared with the third term. Under these conditions, the cubic equation (20) can be replaced by a simpler quadratic and the proportions of Cu^{2+} and CuA calculated from eqns. (21)—(23):

$$[Cu^{2+}] = [Cu_c]/(1+y) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

where

$$y = K_1\{-b \pm \sqrt{(b^2 + 4f_1^2f_2^3[H^+]^2[A]_o/K_1)}\}/(2f_1^2f_2[H^+]^2) \quad . \quad . \quad (22)$$

where

$$b = (f_1^2f_2[H^+]^2/K_1) - f_2^2([A_o] - [Cu_o]) \quad . \quad . \quad . \quad . \quad . \quad (23)$$

Equations (21)—(23) require only a knowledge of the equilibrium constant K_1 and are independent of a knowledge of the dissociation constants of catechol. Table 7 shows that

[10] Dobbie, Kermack, and Lees, *Biochem. J.*, 1955, **59**, 240.

TABLE 7. *Distributions of cupric ions and complexes.*

Solutions of 10 ml. of 0·010M-catechol, 1 ml. of 0·01047M-$Cu(NO_3)_2,3H_2O$, 1 ml. of 0·50M-KNO_3, and 0·2 ml. of 0·2% gelatin, with (*a*) no addition; (*b*) addition of 0·4 ml. of NaOH (0·01N); (*c*) addition of 1·0 ml. of NaOH (0·01N); (*d*) addition of 1·6 ml. of NaOH (0·01N).

						Eqns. (19)—(20)			Eqns. (21)—(23)		Plrgrphy
	$10^3[A_o]$	$10^3[Cu_o]$	10^3I	pH	$[A^{2-}]$	Cu^{2+} (%)	CuA (%)	CuA_2^{2-} (%)	Cu^{2+} (%)	CuA (%)	Cu^{2+} (%)
(*a*)	8·196	0·858	41·0	4·53	$10^{-14·97}$	96·6	3·4	<0·001	96·6	3·4	98
(*b*)	7·936	0·831	40·0	5·06	$10^{-13·94}$	72·7	27·3	0·01	72·7	27·3	78
(*c*)	7·575	0·793	37·8	5·35	$10^{-13·41}$	43·2	56·7	0·08	42·9	57·1	44
(*d*)	7·246	0·759	36·3	5·71	$10^{-12·72}$	13·1	86·4	0·5	13·3	86·7	16

the percentages of Cu^{2+} and CuA, in a number of solutions, given by these equations are in excellent agreement with those given by equations (19)—(20). Moreover, the percentages of Cu^{2+} calculated are in good agreement with those found polarographically.

EXPERIMENTAL

The potentiometric measurements were made with a Doran Universal pH meter and D.C. potentiometer with Doran micro-calomel and " Alkacid " glass electrodes set at 0·05M-potassium phthalate = pH 4·005 at 25°. The linearity of the glass electrode over the pH range measured was confirmed with the hydrogen electrode and also with the following buffer solutions: 0·025M-KH_2PO_4–0·025M-Na_2HPO_4, pH 6·85; 0·05M-borax, pH 9·18; and the Britton–Welford buffer 0·2N-KH_2PO_4–0·2N-NaOH, pH 10·74—11·56. At the end of each titration the pH meter invariably returned to within 0·01 pH unit of the pH of the phthalate buffer. All pH measurements were made at 25° ± 0·1°. A stream of purified nitrogen was used to stir the solutions and maintain an inert atmosphere.

The polarographic measurements were made with a Tinsley pen recording polarograph and dropping mercury electrode. For most determinations the voltage span of the instrument was reduced from 3·0 v to 0·9 v so that when the potentiometer was run slowly, potentials could be measured to ±1·5 mv. The Doran potentiometer, reading to 0·1 mv, was used to check the applied potential and, in conjunction with a standard resistance, the current indicated by the pen deflections. Current measurements were made on damped waves except in the experiment with phosphate buffers pH 7—8, when values were taken from the tops of the undamped fluctuations of the recorder.[11] The Tinsley polarographic cell was connected by a saturated potassium nitrate agar bridge to a saturated calomel electrode and all potentials quoted refer to this electrode. In the experiment with phosphate buffers pH 7—8, the total internal resistance was 1400 ohms and corrections for the iR drop through the cell were made when plotting $\log i/(i_d - i)$ against potential. The cell temperatures were maintained at 25° ± 0·1°. Purified nitrogen was used for degassing the solutions.

" AnalaR " salts were used, and cupric nitrate solution was analysed iodometrically for copper. Catechol was resublimed (m. p. 104°). The alkali solutions were carbonate-free and boiled-out glass-distilled water was used throughout.

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UNIVERSITY OF BRISTOL, LONG ASHTON, BRISTOL. [*Recieved, July 15th*, 1957].

[11] Gelles and Nancollas, *J.*, 1956, 4847.

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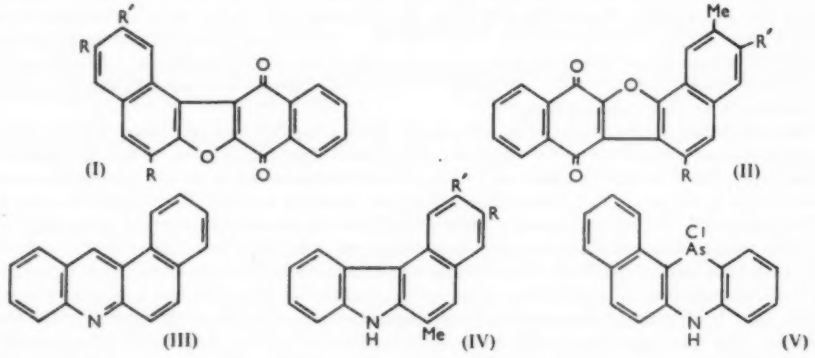
998. ***Carcinogenic Nitrogen Compounds. Part XXIII.* New Polymethylated Homologues of 3 : 4-Benzacridine and 3 : 4-Benzocarbazole, and Related Compounds.***

By Ng. Ph. Buu-Hoï, P. Jacquignon, and C. T. Long.

The synthesis is reported of several penta- and hexa-methyl-3 : 4-benzacridines, dimethyl-3 : 4-benzocarbazoles, and tetra- and penta-methyl homologues of 10-chloro-5 : 10-dihydro-1 : 2-benzophenarsazine, for test as carcinogens; in connexion with these syntheses, the chemistry of several mono- and di-methylnaphthols has been investigated.

Although, unlike the corresponding compounds in the 1 : 2-benzacridine series,[1] mono- and di-methyl-3 : 4-benzacridines have, with a few exceptions, been found to be non-carcinogenic, some trimethyl-3 : 4-benzacridines have shown pronounced carcinogenic activity.[2] This suggested an investigation of the influence on carcinogenicity due to a further increase in the number of methyl groups; accordingly, some of the 462 possible pentamethyl- and the 462 possible hexamethyl-3 : 4-benzacridines have been prepared.

Convenient intermediates are dimethyl-2-naphthols, some of which have now been thoroughly investigated. 3 : 6-, 3 : 7-, and 6 : 7-Dimethyl-2-naphthol were prepared from 2 : 6-, 2 : 7-, and 2 : 3-dimethylnaphthalene *via* the sulphonic acids,[3] and found to



condense readily with 2 : 3-dichloro-1 : 4-naphthaquinone, giving brasanquinones[4] (I), a reaction which provides further proof of the position occupied by the hydroxy-group in these three naphthols. Further, it was confirmed that sulphonation of 2 : 6-dimethylnaphthalene at low temperature yields the 4-sulphonic acid, whereas 1 : 6-dimethylnaphthalene gave only the 4-sulphonic acid at both high and low temperature. 3 : 7- and 4 : 7-Dimethyl-1-naphthol, prepared from these sulphonic acids, reacted with 2 : 3-dichloro-1 : 4-naphthaquinone to give the brasanquinones (II), proof that the β-position adjacent to the hydroxy-group was free.

Among the pentamethyl derivatives of 3 : 4-benzacridine (III), the 1 : 6 : 7 : 9 : 3′- and 6 : 7 : 9 : 2′ : 3′-derivative were obtained by Ullmann–Fetvadjian condensation[5] of 3 : 7- and 6 : 7-dimethyl-2-naphthol with 3 : 4 : 5-trimethylaniline and paraformaldehyde. 3 : 7-Dimethyl-*N*-(3 : 4-dimethylphenyl)-2-naphthylamine, resulting from a Knoevenagel

* Part XXII, *J.*, 1957, 3126.

[1] See Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[2] Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22.
[3] Weissgerber and Kruber, *Ber.*, 1919, **52**, 346, 367; Coulson, *J.*, 1935, 77.
[4] Cf. Buu-Hoï, *J.*, 1952, 489; Buu-Hoï and Demerseman, *J.*, 1952, 4699.
[5] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.

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condensation [6] of 3 : 7-dimethyl-2-naphthol with 3 : 4-dimethylaniline, underwent a Bernthsen reaction [7] with acetic anhydride, to give 1 : 5 : 7 : 8 : 3′-pentamethyl-3 : 4-benzacridine; the 1 : 5 : 7 : 8 : 2′- and the 5 : 7 : 8 : 2′ : 3′-pentamethyl isomers were similarly prepared from *N*-(3 : 4-dimethylphenyl)-3 : 6- and 6 : 7-dimethyl-2-naphthylamine. In the group of hexamethyl-3 : 4-benzacridines, the 1 : 5 : 6 : 7 : 9 : 2′- and the 5 : 6 : 7 : 9 : 2′ : 3′-isomer were prepared by Bernthsen reactions with 3 : 6- and 6 : 7-dimethyl-*N*-(2 : 4 : 5-trimethylphenyl)-2-naphthylamine.

In the 3 : 4-benzocarbazole group, the 1 : 2′- and 1 : 3′-derivatives (IV) were obtained by a Japp–Maitland condensation [8] of 3 : 6- and 3 : 7-dimethyl-2-naphthol with phenylhydrazine and its hydrochloride. In view of the known oncogenic activity of some 10-chloro-5 : 10-dihydrobenzophenarsazines,[9] the 4 : 7 : 8 : 2′- and 7 : 8 : 2′ : 3′-tetramethyl and the 6 : 8 : 9 : 2′ : 3′-pentamethyl derivative of 10-chloro-5 : 10-dihydro-1 : 2-benzophenarsazine (V) were prepared, by a Wieland–Rheinheimer condensation [10] of arsenic trichloride with the appropriate *N*-aryl-2-naphthylamine.

The benzacridines prepared have not caused tumours to develop during 4 months' test on mice by Dr. Zajdela of this Institute.

Experimental

Dimethylnaphthols.—2 : 6- and 2 : 7-Dimethylnaphthalene were sulphonated at 135—140° with 98% sulphuric acid, and the sulphonic acids obtained were converted into 3 : 7- (m. p. 176·5°; lit., 173—174°) and 3 : 6-dimethyl-2-naphthol (m. p. 173°; lit., 171—172°) by alkaline fusion, according to Weissgerber and Kruber; [3] alkaline fusion of the product of sulphonation of 2 : 6-dimethylnaphthalene at room temperature yielded 3 : 7-dimethyl-1-naphthol (m. p. 104—105°; lit., 105—106°). 4 : 7-Dimethyl-1-naphthol, prepared by alkaline fusion of the sulphonation product of 1 : 6-dimethylnaphthalene, crystallised from light petroleum as colourless needles, m. p. 84° (lit., 82°), b. p. 175—176°/18 mm.

3″ : 7″-*Dimethyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (I; R = R″ = Me, R′ = H).—This *compound* was prepared by refluxing for 10 min. a solution of 3 : 7-dimethyl-2-naphthol (1 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (1·3 g.) in dry pyridine (15 c.c.); the precipitate, formed on cooling, recrystallised from pyridine as orange-yellow needles (1·2 g.), m. p. 269°, giving a turquoise colour in sulphuric acid (Found: C, 80·7; H, 4·1. $C_{22}H_{14}O_2$ requires C, 81·0; H, 4·3%). The 3″ : 6″-*dimethyl isomer* (I; R = R′ = Me, R″ = H), similarly prepared from 3 : 6-dimethyl-2-naphthol, formed orange needles, m. p. 274° (decomp. >262°), from pyridine (Found: C, 80·9; H, 4·1%). The 6″ : 7″-*dimethyl isomer* (I; R = H, R′ = R″ = Me), obtained from 6 : 7-dimethyl-2-naphthol, crystallised as orange needles, m. p. 291°, from pyridine (Found: C, 80·7; H, 4·5%).

3″ : 7″-*Dimethyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-5 : 4)*furan*-1′ : 4′-*quinone* (II; R = Me, R′ = H).—Prepared from 3 : 7-dimethyl-1-naphthol, this *quinone* formed deep yellow needles, m. p. 292°, from pyridine (Found: C, 80·9; H, 4·3%); the 4″ : 7″-*dimethyl isomer* (II; R = H, R′ = Me) formed orange-yellow, sublimable needles, m. p. 350°, from pyridine, giving a deep blue halochromy in sulphuric acid (Found: C, 80·9; H, 4·1%).

1 : 6 : 7 : 9 : 3′-*Pentamethyl*-3 : 4-*benzacridine*.—To a mixture of 3 : 7-dimethyl-2-naphthol (7 g.) and 3 : 4 : 5-trimethylaniline (7 g.) at 250°, paraformaldehyde (3 g.) was added in small portions; after the vigorous evolution of water had subsided, the mixture was refluxed for 5 min. and fractionated *in vacuo*. The portion of b. p. *ca.* 303°/18 mm. was treated in benzene with picric acid, and the picrate recrystallised several times from benzene, giving orange needles, m. p. 183° (decomp. > 162°). Basification with aqueous ammonia furnished the free *acridine*, yellowish prisms (0·8 g.), m. p. 179° (from benzene) (Found: C, 88·0; H, 7·1. $C_{22}H_{21}N$ requires C, 88·3; H, 7·1%). 6 : 7 : 9 : 2′ : 3′-*Pentamethyl*-3 : 4-*benzacridine*, b. p. 289°/13 mm., similarly prepared from 6 : 7-dimethyl-2-naphthol (7 g.), formed yellowish prisms (1·2 g.), m. p. 196°, from benzene (Found: C, 88·6; H, 6·8%), and gave a *picrate*, crystallising as yellow prisms,

[6] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346.
[7] Cf. Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 648; *Rec. Trav. chim.*, 1945, **64**, 251.
[8] Japp and Maitland, *J.*, 1903, **83**, 267.
[9] Lacassagne, Rudali, Buu-Hoï, and Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451.
[10] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1.

m. p. 263° (decomp. > 250° from *o*-dichlorobenzene (Found: N, 10·3. $C_{28}H_{24}O_7N_4$ requires N, 10·6%).

N-(3 : 4-*Dimethylphenyl*)-3 : 7-*dimethyl*-2-*naphthylamine*.—A mixture of 3 : 7-dimethyl-2-naphthol (10 g.) and 3 : 4-dimethylaniline (7 g.) was refluxed for 30 hr. with iodine (0·2 g.), taken up in benzene, washed with dilute aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The solvent was removed, and the residue fractionated *in vacuo*. The *diarylamine* (8 g.) obtained, b. p. 267—268°/16 mm., formed colourless leaflets, m. p. 136°, from ethanol (Found: C, 87·0; H, 7·9. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7%), giving a picrate, crystallising as deep violet needles, m. p. 131°, from ethanol.

10-*Chloro*-5 : 10-*dihydro*-4 : 7 : 8 : 2′-*tetramethyl*-1 : 2-*benzophenarsazine*, prepared by refluxing for 1 hr. a solution of this diarylamine (2 g.) and arsenic trichloride (1·3 g.) in *o*-dichlorobenzene (10 c.c.), crystallised from that solvent as yellow needles (2 g.), m. p. 305° (decomp. > 228°), giving a brown-red halochromy in sulphuric acid (Found: C, 62·7; H, 5·1. $C_{20}H_{19}NAsCl$ requires C, 62·6; H, 5·0%).

1 : 5 : 7 : 8 : 3′-*Pentamethyl*-3 : 4-*benzacridine*.—A mixture of the foregoing diarylamine (5 g.), acetic anhydride (3 g.), and zinc chloride (6 g.) was heated at 185° for 40 hr.; after cooling, the product was treated with hot aqueous sodium hydroxide, and the acridine taken up in benzene, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The portion boiling at 310—320°/18 mm. was converted into a picrate, crystallising as orange-yellow needles, m. p. 289° (decomp. > 226°) from *o*-dichlorobenzene; basification with aqueous ammonia furnished the *acridine* as yellowish needles (1 g.), m. p. 160° (Found: C, 88·1; H, 7·3%).

N-(3 : 4-*Dimethylphenyl*)-3 : 6-*dimethyl*-2-*naphthylamine*.—Prepared from 3 : 6-dimethyl-2-naphthol (10 g.) and 3 : 4-dimethylaniline (7 g.) in the presence of iodine (0·5 g.), this *diarylamine*, b. p. 257—258°/13 mm., formed colourless prisms (8 g.), m. p. 100°, from light petroleum (Found: C, 87·2; H, 7·9%), giving a picrate, crystallising as dark violet needles, m. p. 155° (decomp. > 145°), from ethanol.

1 : 5 : 7 : 8 : 2′-*Pentamethyl*-3 : 4-*benzacridine*, prepared from this amine (5 g.), acetic anhydride (3 g.), and zinc chloride (6 g.), formed yellowish needles (1 g.), m. p. 190°, from ethanol (Found: C, 87·9; H, 7·2%), giving a *picrate*, crystallising from chlorobenzene as orange-yellow leaflets, m. p. 279° (decomp. > 246°) (Found: N, 10·3%).

N-(3 : 4-*Dimethylphenyl*)-6 : 7-*dimethyl*-2-*naphthylamine*.—Obtained as above from 6 : 7-dimethyl-2-naphthol, this *diarylamine*, b. p. 275°/17 mm., formed colourless prisms, m. p. 140°, from ethanol (Found: C, 87·0; H, 7·7%), giving a picrate, crystallising from ethanol as violet-black needles, m. p. 134°.

10-*Chloro*-5 : 10-*dihydro*-7 : 8 : 2′ : 3′-*tetramethyl*-1 : 2-*benzophenarsazine*, prepared from this diarylamine, crystallised as orange-yellow, sublimable needles, m. p. 308°, from chlorobenzene, giving a brown-red halochromy in sulphuric acid (Found: C, 62·4; H, 5·3%). 5 : 7 : 8 : 2′ : 3′-*Pentamethyl*-3 : 4-*benzacridine*, b. p. 306—310°/20 mm., prepared from the same diarylamine, formed yellowish prisms, m. p. 176°, from *cyclo*hexane (Found: C, 88·0; H, 6·7%).

3 : 6-*Dimethyl*-N-(2 : 4 : 5-*trimethylphenyl*)-2-*naphthylamine*.—This *diarylamine* (8 g.), prepared by refluxing for 20 hr. a mixture of 3 : 4 : 5-trimethylaniline (8 g.), 3 : 6-dimethyl-2-naphthol (10 g.), and iodine (0·5 g.), was a pale yellow, viscous oil, b. p. 256—257°/12 mm. (Found: C, 87·5; H, 8·0. $C_{21}H_{23}N$ requires C, 87·2; H, 8·2%), giving a picrate, crystallising as violet-black needles, m. p. 106°, from benzene.

1 : 5 : 6 : 7 : 9 : 2′-*Hexamethyl*-3 : 4-*benzacridine*, b. p. 300°/12 mm., prepared from this diarylamine (5 g.), acetic anhydride (3 g.), and zinc chloride (7 g.), formed pale yellow prisms, m. p. 136°, from acetone (Found: C, 88·5; H, 7·7. $C_{23}H_{23}N$ requires C, 88·2; H, 7·4%), giving a picrate, crystallising from ethanol–benzene as orange prisms, m. p. 167°.

6 : 7-*Dimethyl*-N-(2 : 4 : 5-*trimethylphenyl*)-2-*naphthylamine*.—This *diarylamine* was a pale yellow, viscous oil, b. p. 278—280°/20 mm. (Found: C, 87·0; H, 8·1%), giving a violet-black picrate, m. p. 153—154°, unstable in ethanol.

10-*Chloro*-5 : 10-*dihydro*-6 : 8 : 9 : 2′ : 3′-*pentamethyl*-1 : 2-*benzophenarsazine* (1 g.), prepared from the foregoing diarylamine (2 g.), crystallised as yellow needles, m. p. 265° (decomp. > 240°), from *o*-dichlorobenzene, giving a brown-red halochromy in sulphuric acid (Found: C, 63·0; H, 5·0. $C_{21}H_{21}NAsCl$ requires C, 63·4; H, 5·3%).

5 : 6 : 7 : 9 : 2′ : 3′-*Hexamethyl*-3 : 4-*benzacridine*, b. p. 320—325°/18 mm., prepared from the foregoing diarylamine (5 g.), formed pale yellow needles (0·8 g.), m. p. 198°, from benzene (Found: C, 87·9; H, 7·0%); the corresponding *picrate* crystallised as yellow needles, m. p.

267° (decomp. > 256°), from *o*-dichlorobenzene (Found: N, 9·9. $C_{29}H_{26}O_7N_4$ requires N, 10·3%).

1 : 2′-*Dimethyl*-3 : 4-*benzocarbazole* (IV; R = Me, R′ = H).—A mixture of 3 : 6-dimethyl-2-naphthol (4 g.), phenylhydrazine (4 g.), and phenylhydrazine hydrochloride (4 g.) was refluxed for 90 min., then cooled. 5% Aqueous acetic acid was added, and the product taken up in benzene, washed with water, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The portion boiling at 280—285°/12 mm. was recrystallised twice from light petroleum, forming colourless leaflets (1 g.), m. p. 182° (Found: C, 87·8; H, 6·3. $C_{18}H_{15}N$ requires C, 88·1; H, 6·2%), giving a picrate, crystallising as violet-brown needles, m. p. 208° (decomp. > 190°), from ethanol.

1 : 3′-*Dimethyl*-3 : 4-*benzocarbazole* (IV; R = H, R′ = Me), similarly prepared from 3 : 7-dimethyl-2-naphthol, formed colourless leaflets (0·6 g.), m. p. 149°, from light petroleum (Found: C, 87·9; H, 6·3%), giving a picrate, violet-brown needles, m. p. 210° (decomp. > 160°), from ethanol.

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THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, July 22nd*, 1957.]

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999. *Potential Antimalarial Derivatives of Triaza-anthracene.*

By D. M. BESLY and A. A. GOLDBERG.

An analogue of mepacrine containing the 1 : 3 : 10-triaza-anthracene nucleus has been synthesised but has no antimalarial activity.

THE quinoline derivatives pamaquine and primaquin, in which the (dialkyl)aminoalkylamino-side-chain is *peri* to a ring-nitrogen atom are the only known antimalarials [1] which are effective against the secondary exo-erythrocytic stages of the parasite reponsible for relapse in human *P. vivax* infections. The possibility was entertained that 1 : 3 : 10-triaza-anthracenes of type (I; R = OMe, R′ = H or OMe), because of the *peri* situation of the side-chain to a ring-nitrogen atom, might combine the schizonticidal activity of the acridine derivative, mepacrine, with the radically curative properties of pamaquine. Recently, a derivative (" Azacrin ") of 1 : 10-diaza-anthracene [2] has been shown to be a very effective schizonticide in human malaria due to *P. falciparium* [3,4] *and P. vivax*; [5] it has a shorter pyrexia- and parasite-clearance time, and allows fewer relapses, than mepacrine or chloroquin. Up to the present, however, the possibility of determining whether " Azacrin " has radically curative properties against *P. vivax* disease has not presented itself.

A further point of interest arises from Madinaveitia's hypothesis that antimalarials function by virtue of their ability to antagonise riboflavin, an essential factor for the survival of the parasite. 1 : 3 : 10-Triaza-anthracenes are more closely related to riboflavin than is mepacrine and might therefore be expected to be superior flavin antagonists.

A derivative of 2 : 4 : 10-triaza-anthracene [7] has been found to be inactive; this is not surprising since the situation of the dialkylaminoalkylamino-group in the 3- and not in the 9-position of the ring, gives the compound no formal resemblance to mepacrine.

Three approaches have been made to the desired compounds. 5-Bromo-2-methylpyrimidine-4-carboxylic acid was condensed with aniline to give 5-anilino-2-methylpyrimidine-4-carboxylic acid; and 2 : 4-dichlorobenzoic acid was condensed with 5-amino-2-methoxypyrimidine to give 4-chloro-2-(2-methoxy-5-pyrimidylamino)benzoic acid (II;

[1] Report by Council on Pharmacy and Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558.
[2] Besly and Goldberg, *J.*, 1954, 2448.
[3] Bruce-Chwatt and Archibald, *Brit. Med. J.*, 1953, **7**, 539.
[4] Ang'awa and Fendall, *J. Trop. Med. Hyg.*, 1954, **57**, 59.
[5] Pasquel, *Rev. Inst. Salubridad y Enfermedades Trop.*, 1955, **15**, 51.
[6] Madinaveitia, *Biochem. J.*, 1946, **40**, 373.
[7] King and King, *J.*, 1947, 726.

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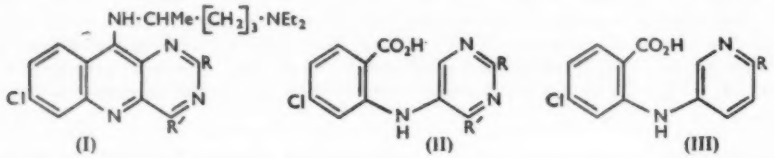
R = OMe, R′ = H). Although both acids were obtained in acceptable yield neither would undergo the Magidson–Grigorovski cyclisation with phosphorus oxychloride to give the *meso*-chlorotriaza-anthracene necessary for the introduction of the side-chain.

The presence of $-I$, $-M$ groups in the non-carboxylated ring of 2-carboxy-diphenylamine or diphenyl ether increases the energy of activation [8] of the cyclisation process. In acids of this type in which the non-carboxylated ring is replaced by a pyridine ring



(I) (II) (III)

(III; R = H) the $-I$ effect of the protonised ring-nitrogen atom (in the acid cyclising agent) prevents [2] cyclisation unless there is present a $+M$ group (alkoxyl) in the position R. Although the $+E$ effect of this alkoxy-group cannot *directly* increase the electron-density at the position of cyclisation it appears that the mesomerism of the protonised cyclic imidate grouping in such compounds can cause partial bond-localisation and suppress the inductive and tautomeric mechanisms by which the nitrogen atom normally creates electron defect at neighbouring carbon atoms. In this connexion it is noteworthy that, while pyridine is much more resistant to electrophilic attack than nitrobenzene,[9] the ease [10] of electrophilic substitutions becomes comparable with that of benzene when the pyridine nucleus contains a $+M$ substituent in the 2- or 4-position. In pyrimidines, the ability to undergo electrophilic attack at position 5, completely suppressed in pyrimidine itself, reappears [11] when the nucleus contains a $+M$ group in *both* the 2- and the 4-position.

It therefore seemed that the difficulties might be surmounted by the use of an amino-pyrimidine containing *two* $+M$ groups which might be expected to neutralise the $-I$ effects of the two pyrimidine ring-nitrogen atoms. Accordingly 2 : 4-dichlorobenzoic acid was condensed with 5-amino-2 : 4-dimethoxypyrimidine, 5-amino-2 : 4-diphenoxy-pyrimidine, and 5-aminouracil, to give the acids (II; R = R′ = OMe, OPh, and OH respectively). Treatment of acid (II; R = R′ = OMe) with phosphorus oxychloride effected cyclisation in good yield but unfortunately with loss of one (presumably the 4-) methoxy-group.

The same was observed with the acid (II; R = R′ = OPh), one phenoxy-group being lost. With the acid (II; R = R′ = OH) 2 : 4 : 6 : 9-tetrachloro-1 : 3 : 10-triaza-anthracene was obtained but could not be isolated in the pure state; when, however, the crude material was heated with phenol and 4-diethylamino-1-methyl-*n*-butylamine, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-4(or 2)-hydroxy-2(or 4)-phenoxy-1 : 3 : 10-triaza-anthracene (I; R = OPh, R′ = OH) was obtained in the form of the phosphate. It is evident that, in addition to the replacement of the *meso*-substituent by a phenoxy-group, followed by normal reaction of the phenoxy-group with the dialkylaminoalkylamine, one of the chloro-groups in the pyrimidine nucleus has also been replaced and the other hydrolysed during isolation of the product.

Antimalarial Activity.—Daily oral dosage of 100 mg./kg. of compound (I; R = OPh, R′ = OH) for 3 consecutive days gave no significant protection to 50 g. chicks infected intravenously on day 0 with 20×10^6 *P. gallinaceum* merozoites. All the infected birds had a 40—50% blood parasitæmia on day 5, death ensuing on day 6—8. Chicks similarly infected and given 25 mg./kg. of mepacrine daily for 3 days were only 0—5% parasitised

[8] Goldberg, in preparation.
[9] Elderfield, "Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, pp. 408 *et seq.*
[10] Maier-Bode, "Das Pyridin und seine Derivate," Knapp, Halle, Saale, 1934.
[11] Lythgoe, *Quart. Rev.*, 1949, **3**, 181.

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on day 5 and survived until day 14—18. It is believed that the lack of antiplasmodial activity in this compound is due to the presence of the 4-hydroxyl group which by virtue of the hydroxypyrimidine–dihydropyrimidone tautomerism at the 3 : 4-position removes aromatic character from the compound.

Experimental

5-Aminouracil.—The following method was easier than that using ferrous sulphate.[12] Sodium dithionite (200 g.) was added in one lot to a stirred suspension of 5-nitrouracil (42 g.) in water (670 c.c.) and ammonia (*d* 0·88; 27 c.c.). The mixture developed heat and the salt slowly dissolved; more ammonia was added from time to time to maintain pH 8·5. When the reaction was finished, as shown by constancy of pH, the mixture was set aside. The precipitate was collected and dissolved in cold water (400 c.c.) and 2N-hydrochloric acid (150 c.c.), the solution filtered (charcoal) and basified with ammonia, and the precipitate of 5-aminouracil (31 g., 91%) collected and dried at 40°.

2 : 4-*Dimethoxy-5-nitropyrimidine.*—2 : 4-Dichloro-5-nitropyrimidine [13] (17·7 g.) was added portionwise to a stirred solution of sodium (4·3 g.) in methanol (80 c.c.) at 0—5°. The mixture was kept at room temperature overnight, then refluxed for 4 hr., and poured on ice-water (500 c.c.). The *ether* (15·6 g., 92%; m. p. 90°) was collected, washed with water, and dried at 35°; this was pure enough for further use. A sample crystallised from methanol in pale orange needles, m. p. 94—96° (Found: N, 23·4. $C_6H_7O_4N_3$ requires N, 22·7%).

2 : 4-*Dimethoxy-5-aminopyrimidine.*—(*a*) The foregoing nitro-compound (1·85 g.) was hydrogenated in methanol (50 c.c.) at 30°/760 mm. over 10% palladium–charcoal; absorption was rapid and ceased at the theoretical uptake. Evaporation of the filtered mixture gave the required *amine* (1·4 g., 91%) as a pink solid, m. p. 86—88°; this separated from ligroin (b. p. 60—80°) in colourless needles of the same m. p. (Found: N, 27·4. $C_6H_9O_2N_3$ requires N, 27·1%).

(*b*) 2 : 4-Dimethoxy-5-nitropyrimidine (35 g.) was added portionwise during ½ hr. to a stirred, refluxing mixture of alcohol (160 c.c.), water (160 c.c.), acetic acid (4 c.c.), and Pacteron iron powder (from Staveley Iron Co.) (60 g.). After a further 2 hours' refluxing the mixture was adjusted to pH 8·0 with saturated aqueous sodium carbonate, then, after addition of potassium hydrogen carbonate (20 g.), refluxed with stirring for a further 2 hr. and filtered, and the solid residue washed into the filtrate with boiling alcohol (400 c.c.). The filtrate was evaporated to small volume at reduced pressure and the residue subjected to continuous ether-extraction for 7 hr. Distillation of the ether left the base as a mauve crystalline mass (27 g., 92%), m. p. 86°.

5-*Nitro*-2 : 4-*diphenoxypyrimidine.*—A mixture of phenol (47 g.) and xylene (500 c.c.) was stirred and part (40 c.c.) of the xylene distilled off to remove moisture. The mixture was cooled, sodium (11·5 g.) added in one lot, stirring continued on the water-bath until the metal had dissolved (1 hr.), and the mixture chilled. 2 : 4-Dichloropyrimidine (40 g.) was added portionwise during 20 min. and the mixture stirred at 5° for a further hour. After being kept at room temperature overnight the mixture was heated on the water-bath for 4 hr., cooled, and poured into excess of water. The xylene layer was separated and washed with water, and the xylene distilled off at reduced pressure. Crystallisation of the residue from ligroin (b. p. 60—80°; 500 c.c.) gave the *product* (52 g., 83%) as brown prisms, m. p. 104—106°; a sample crystallised from benzene–ligroin in colourless prisms, m. p. 108—110° (Found: N, 13·5. $C_{16}H_{11}O_4N_3$ requires N, 13·6%).

5-*Amino*-2 : 4-*diphenoxypyrimidine.*—The foregoing nitro-compound (31 g.) was reduced in the same manner as the dimethoxy-compound, with alcohol (100 c.c.), water (100 c.c.), acetic acid (4 c.c.). and iron powder (40 g.). The filtrate from the iron oxide cake and the alcohol washings (500 c.c.) were combined, diluted with ice-water (3 l.), and refrigerated overnight. The 5-*amino*-2 : 4-*diphenoxypyrimidine* (23 g., 82%; m. p. 126—128°) was collected and dried at 80°; a sample separated from benzene–ligroin (b. p. 60—80°) as a powder, m. p. 130—132° (Found: N, 14·9. $C_{16}H_{13}O_2N_3$ requires N, 15·0%).

4-*Chloro*-2-(2 : 4-*dimethoxy-5-pyrimidyl*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (28·4 g.,

[12] Johnson and Matsuo, *J. Amer. Chem. Soc.*, 1919, **41**, 784.
[13] Whitaker, *J.*, 1951, 1568.

0·148 mol.), anhydrous potassium carbonate (10·3 g., 0·074 mol.), 5-amino-2 : 4-dimethoxypyrimidine (23 g., 0·148 mol.), pentyl alcohol (150 c.c.), and a trace of cupric oxide were stirred at the b. p. for 3 hr., water being removed in a Dean and Stark trap. Water (250 c.c.) and potassium carbonate (11 g.) were added, the alcohol removed in steam, and the filtered solution (charcoal) acidified to bromocresol-green with 10% acetic acid. The glutinous precipitate was collected and dissolved in water (150 c.c.) and the minimum amount of sodium hydrogen carbonate, and the hot solution poured into a solution of sodium chloride (100 g.) in hot water (250 c.c.). The sodium salt separated as a red oil which slowly solidified. This was collected, dissolved in boiling water (100 c.c.), and filtered (charcoal) and the hot solution was acidified with 10% acetic acid to give the *product* as a mauve powder (24 g., 52%), m. p. 186—190°. Crystallisation from *n*-butyl acetate (200 c.c.) gave a purer acid (14 g.), m. p. 202—204°, together with a further 7 g. of lower m. p. from the mother-liquor. The analytical sample separated from the same solvent in colourless flakes, m. p. 208—210° (Found: *M*, 306; N, 14·2; Cl, 11·8%. $C_{13}H_{13}O_4N_3Cl$ requires *M*, 309·5; N, 13·6; Cl, 11·5%).

4-*Chloro*-2-(2 : 4-*dihydroxy*-5-*pyrimidyl*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (38·2 g., 0·2 mol.) was added to a solution of potassium carbonate (13·8 g., 0·1 mol.) in water (400 c.c.), and the resulting solution adjusted to pH 7·0. 5-Aminouracil (25·4 g., 0·2 mol.), copper bronze (0·5 g.), and cupric oxide (0·25 g.) were added, and the mixture was stirred at the b. p. for 6 hr. and filtered hot. The solid was stirred with *ca.* 0·01N-hydrochloric acid (200 c.c.) to remove adhering 5-aminouracil, filtered, washed with water, and then suspended in hot water (350 c.c.), and sufficient sodium hydrogen carbonate was added to effect dissolution. Sodium chloride (80 g.) was added to the stirred solution whence the crystalline sodium salt was soon precipitated. Next morning the precipitate was collected and dissolved in boiling water (750 c.c.), and the solution acidified with acetic acid (30 c.c.) and digested on the water-bath to effect coagulation of the precipitated acid. The *acid* was obtained as a cream powder (16·6 g., 30%), m. p. 350—352° (decomp.) [Found: *M* (by electrometric titration), 283; N, 15·1; Cl, 12·4%. $C_{11}H_9O_4N_3Cl$ requires *M*, 281·5; N, 14·9; Cl, 12·6%).

4-*Chloro*-2-(2 : 4-*diphenoxy*-5-*pyrimidylamino*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (9·6 g., 0·05 mol.), potassium carbonate (3·5 g., 0·025 mol.), 5-amino-2 : 4-diphenoxypyrimidine (14 g., 0·05 mol.), pentyl alcohol (100 c.c.), and a trace of copper oxide were stirred at the reflux for 5 hr. After removal of the alcohol, potassium carbonate (4 g.) was added and the solution filtered (charcoal) and acidified with 20% acetic acid. The resinous precipitate was collected and triturated with hot toluene (15 c.c.) until it crystallised. After being kept overnight the crystals were drained and recrystallised from methanol (100 c.c.), to give the pure *acid* as colourless needles (5·0 g., 23%), m. p. 196—198° (Found: *M*, 433; N, 9·9; Cl, 8·1%. $C_{23}H_{16}O_4N_3Cl$ requires *M*, 433·5; N, 9·7; Cl, 8·2%).

6-*Chloro*-2 : 4-*dihydroxy*-1 : 3 : 10-*triaza*-*anthr*-9-*one*.—4-Chloro-2-(2 : 4-dihydroxy-5-pyrimidylamino)benzoic acid (5·6 g.) was heated on the water-bath with 90% sulphuric acid (60 c.c.) for 1½ hr., then poured on crushed ice (200 g.). After digestion on the water-bath for 2 hr. the precipitate was collected, washed with water, and dried. The yellow powder (4·0 g., 76%) thus obtained contained sulphur, presumably as a sulphonic acid; it was desulphonated by 90% orthophosphoric acid (130 g.) at 160° for 3 hr., the whole being poured into water. The insoluble precipitate of *triaza-anthrone* (3·4 g.) was washed with water and obtained as a yellow powder, free from sulphur, m. p. >400° (Found: N, 16·1; Cl, 13·6. $C_{11}H_6O_3N_3Cl$ requires N, 15·9; Cl, 13·4%).

6-*Chloro*-9-(4-*diethylamino*-1-*methylbutylamino*)-4(or 2)-*hydroxy*-2(or 4)-*phenoxy*-1 : 3 : 10-*triaza-anthracene Phosphate*.—4-Chloro-2-(2 : 4-dihydroxy-5-pyrimidylamino)benzoic acid (2·8 g.) was refluxed with phosphoryl chloride (28 c.c.) for 24 hr. Excess of phosphoryl chloride was distilled off at reduced pressure, the residue dissolved in phenol (25 g.), and the solution heated for 2 hr. at 110°. 5-Diethylamino-1-methylbutylamine (1·6 c.c.) was added, and the mixture heated for a further 1½ hr. at 110°, and poured into acetone (200 c.c.) containing 10N-hydrochloric acid (2 c.c.). The small precipitate was removed, the filtrate diluted with excess of dry ether, and the glutinous precipitate separated and triturated with a little water until it solidified. The buff-yellow product (1·4 g., 24%) had m. p. >320°; crystallisation from dioxan gave the pure *phosphate* as a bright yellow powder (1·0 g.), m. p. >320° (Found: N, 12·1; Cl, 6·25; P, 5·1. $C_{26}H_{30}O_9N_5Cl,H_3PO_4$ requires N, 12·1; Cl, 6·15; P, 5·35%).

5-*Anilino*-4-*carboxy*-2-*methylpyrimidine*.—5-Bromo-4-carboxy-2-methylpyrimidine (10·9 g.) and potassium carbonate (11 g.) were stirred with aniline (30 c.c.), pentyl alcohol (70 c.c.), and

a trace of copper–copper iodide catalyst at 132—140° for 5 hr. After removal of the alcohol in steam, the residual solution was filtered to remove tar, and the filtrate acidified to pH 4 with sulphuric acid. Crystallisation of the precipitate (4·0 g.; m. p. 212°) from aqueous-alcoholic dioxan gave the acidic *product* (3·2 g.) as yellow needles, m. p. 218° [Found: *M* (by titration), 231; *N*, 18·2%. $C_{12}H_{11}O_3N_3$ requires *M*, 229; N, 18·4%].

Treatment of this acid with phosphoryl chloride did not give a *meso*-chlorotriaza-anthracene; a dark insoluble material, difficult to purify, was obtained which was presumably the crude triazanthrone.

4-Chloro-2-(2-methoxy-5-pyrimidylamino)benzoic Acid (III; R = OMe, R′ = H).—2 : 4-Dichlorobenzoic acid (5·75 g.), potassium carbonate (4·2 g.), 5-amino-2-methoxypyrimidine (3·0 g.), and a trace of copper–copper oxide catalyst were refluxed with pentyl alcohol (25 c.c.) for 3 hr. The alcohol was removed in steam, and the residual solution filtered (charcoal) and adjusted to pH 4·0 with hydrochloric acid. The precipitate was extracted with boiling alcohol (125 c.c.), the filtered solution refrigerated, and the precipitate (1·0 g.; m. p. 230°) collected. Crystallisation from ethyl acetate gave the *product* as colourless leaves, m. p. 236° (Found: *M*, 277; N, 15·2; Cl, 12·7%. $C_{12}H_{10}O_3N_3Cl$ requires *M*, 279·5; N, 15·0; Cl, 12·7%).

Attempts to cyclise this acid failed. For example, the acid (2 g.) with boiling phosphoryl chloride (30 c.c.) for 3 hr. gave an amorphous brown solid, insoluble in acetone, benzene, or ligroin, and this could not be purified.

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1000. *Photo- and Semi-conductance in Organic Crystals. Part V.* Ionized States in Molecular Crystals.*

By L. E. LYONS.

The occurrence of ionized states in a molecular crystal such as naphthalene is discussed. Such states are estimated to lie at energy levels accessible with visible and ultraviolet light. The transition probability to the state in which the electron is transferred to the nearest neighbour corresponds to $f \approx 10^{-6}$. The importance of such states to crystal spectroscopy and to photo- and semi-conduction is considered.

PHOTOCONDUCTION in crystals such as anthracene in dry air is predominantly [1] a surface effect, but there has also been observed [2] a small but definite bulk photoconductivity which is possibly an intrinsic property of the crystal. The theory of light absorption by such crystals has been based [3] upon neutral excitation waves, in which the excitation is transferred from molecule to molecule throughout the crystal and has successfully explained many dominant features of the crystal absorption spectrum at the longer wavelengths, *e.g.*, the relation [3] to the single-molecule spectrum, the Davydov splitting, and the intensity of absorption. Since a neutral excitation wave is not associated with conductivity, we must now ask what is the possibility of obtaining ionized excited electronic states as a result of light absorption. Extrinsic, surface, and secondary effects are neglected at present. Certain of the results have been summarized in a preliminary report.[4]

Excited electronic states of a molecular crystal can be described, on the usual

* Part IV, *J.*, 1957, 3661.

[1] Part I, Bree, Carswell, and Lyons, *J.*, 1955, 1728.
[2] Part III, Lyons and Morris, *J.*, 1957, 3648; Compton, Schneider, and Waddington, *J. Chem. Phys.*, 1957, **27**, 160.
[3] Craig, *J.*, 1955, 2302; Craig and Hobbins, *J.*, 1955, 539; Bree and Lyons, *J.*, 1956, 2662.
[4] Lyons, *Austral. J. Chem.*, 1957, **10**, 365.

assumptions, in several ways (N is the number of molecules in the crystal, $\boldsymbol{\rho}_n, \boldsymbol{\rho}_m, \boldsymbol{\rho}_p$ are position vectors of a molecule, and $\mathbf{K}$ is the excitation wave vector):

(*a*) *Neutral excitation wave.*

$$\mathrm{X}(\mathbf{K}) = N^{-\frac{1}{2}} \sum_1^N{}_n [\exp(i\mathbf{K}.\boldsymbol{\rho}_n)] P_n$$

where, if ϕ_m, ϕ_n' denote unexcited and excited molecule wave functions on sites $\boldsymbol{\rho}_m$, $\boldsymbol{\rho}_n$

$$P_n = \phi_1\phi_2\phi_3 \ldots \phi_{n-1}\phi_n'\phi_{n+1} \ldots \phi_N$$

(*b*) *Ionized excitation wave.*

$$\mathrm{X}(\mathbf{K},\mathbf{r}) = N^{-\frac{1}{2}} \sum_1^N{}_m [\exp(i\mathbf{K}.\boldsymbol{\rho}_m)] Q_{m,m+r}$$

where, if ϕ_m^+, ϕ_{m+r}^- denote wave functions of molecules on sites $\boldsymbol{\rho}_m$, $\boldsymbol{\rho}_{m+r}$, which have lost and gained an electron,

$$Q_{m,m+r} = \phi_1\phi_2 \ldots \phi_{m-1}\phi_m^+\phi_{m+1} \ldots \phi_{m+r}^-\phi_{m+r+1} \ldots \phi_N$$

Here site $\boldsymbol{\rho}_{m+r}$ is separated by a distance $\mathbf{r}$ from site $\boldsymbol{\rho}_m$.

(*c*) *Ionized state with free electrons.* Here the motion of the excited electron is independent of the motion of the hole. Bloch functions become more appropriate as the energy of the excited state increases. The excited electron is described by a function of the type

$$b(\boldsymbol{\lambda}) = N^{-\frac{1}{2}} \textstyle\sum_p [\exp(i\boldsymbol{\lambda}.\mathbf{p})]\, f_p'$$

where $\boldsymbol{\lambda}$ is the wave vector of the excited electron and f_p' the one-electron function of the excited electron at centre $\mathbf{p}$. For a completely free electron f_p' is a constant; otherwise f_p' may be a highly excited molecular orbital, in which case this ionized state with free electrons may be built of excitation waves having all possible values of $\mathbf{r}$, including $\mathbf{r} = 0$. The wave function of the hole can be written in terms of Bloch orbitals for each electron in the ground state, where in each case the Bloch orbital can be expressed in terms of the individual one-electron molecular orbitals. A wave-vector will be associated with the motion of the hole and will differ according to which electron is excited.

$\mathrm{X}(\mathbf{K})[\equiv\mathrm{X}(\mathbf{K},0)]$ and $\mathrm{X}(\mathbf{K},\mathbf{r})$ can be constructed for each excited molecular function. Since for a given level of the excited molecule each $\mathrm{X}(\mathbf{K},\mathbf{r})$ will have a different energy, depending upon both $\mathbf{K}$ and $\mathbf{r}$, there is a great number of possible energy levels in the crystal. In addition there is a near-continuum of levels in which the electron is free. The position is somewhat simplified by considering only optically accessible states, for which $\mathbf{K} \approx 0$.

Exact quantum mechanical calculations being very difficult, however, we now consider the energies of the various ionized levels in anthracene and naphthalene crystals, using approximate classical methods.

(i) *Energies of Free-electron States.*—Compare the energy, I, needed to ionize a ground-state molecule in a crystal with the energy, I_g, of ionization in the gas phase. Ionization in the crystal is regarded as the withdrawal of the electron to a distant point still within the crystal, at which the electron is not specifically attached to any one molecule. A difference between I and I_g arises from the effect of the charges, both positive and negative, which polarize the surrounding region of the crystal. An average polarizability, α, may be attributed to each anthracene molecule. The anisotropic components of α do not appear to be known. For naphthalene estimates have been made [5] and rough values can be deduced for anthracene. The polarization energy, W, arising from a singly-charged positive ion on one site can be calculated from the known crystal structure by summing the contributions from all the surrounding molecules. Since W falls off as $(1/S^4)$, where S is the separation of

[5] Le Fèvre and Le Fèvre, *Rev. Pure Appl. Chem.*, 1955, **5**, 261.

the charged and neutral molecule, the sum over all the surrounding region quickly converges. If α is taken as 15 Å^3, the error can be shown not to exceed 30%. Since [6] $W = -[\alpha e^2/2S^4]$ the nearest four neighbours in the (001) plane contribute −0·58 ev to W, and the nearest 18, −0·88ev. Molecules in adjacent planes also contribute a little, and so $W = -1{\cdot}0 \pm 0{\cdot}3$ ev. In comparison with the error due to the method itself (which is expected to underestimate W), the error (<4%) due to neglecting the polarizability of the positive ion is negligible. For naphthalene $W = -0{\cdot}8 \pm 0{\cdot}3$ ev. For the polarization due to a free electron it seems best to take the same value as for a positively charged molecule. Using $I = I_g - 2W$, we find $I = 5{\cdot}2 \pm 0{\cdot}6$ ev for anthracene and $6{\cdot}5 \pm 0{\cdot}6$ ev for naphthalene. The energy necessary to liberate an electron from the crystal should be given by $I_g - W$, *i.e.*, 6·2 ev for anthracene and 7·3 ev for naphthalene. Photoemission from anthracene is therefore expected at about 2000 ± 100 Å; the experimental value is 2200 Å. In naphthalene emission is expected at about 1700 Å. Free electrons should be produced within the crystal by radiation of wavelength 2400 ± 200 Å for anthracene and 1900 ± 200 Å for naphthalene.

(ii) *Energies of Bound Levels of Large Orbital Radius.*—The relation between the ionization potentials I' and I_g' of an excited molecule in gas and crystal is given [7] approximately by $I' = I_g'(1/\epsilon^2)$, where ϵ is the bulk dielectric constant equal to the square of the refractive index, provided that the excited electron before ionization is in an orbital which is large enough to encompass several neighbouring sites. The change in polarization of the crystals as ionization proceeds is very much smaller than the value calculated for ground-state ionization and may therefore be neglected. For simplicity an average dielectric constant (as for an isotropic crystal) is assumed, but this restriction is easily removed if desired. The orbitals which can be treated in this way are the Rydberg orbitals. The energy range over which they occur is reduced from 2—3 ev in the gas to *ca.* 0·2 ev in the crystal, where they occur just below the ionization limit, I. Rydberg levels with $n = 3$ are irregular in gaseous spectra and of relatively small size so that they should be excepted from the applications of this method. Closely spaced Rydberg levels have not been observed in organic crystals but have been observed [8] both in absorption and fluorescence in some inorganic crystals, where they presumably indicate neutral highly excited waves.

(iii) *Energies of Ionized Exciton States.*—Anthracene and other aromatic molecules, except benzene, have been shown [9] to have a positive electron affinity, A. Consequently a free electron in the crystal may be trapped by a molecule in its path. The existence of positively and negatively charged molecules has already been suggested [2] to explain some features of photoconduction. Let us consider the energy of a state in which the electron has been removed from one molecule in a unit cell to its neighbour. This will be the ionized state of lowest energy. All others in which the separation of positive and negative charge is greater will have energies between this value and I. A cycle, such as was applied [10] to the energies of alkali halide crystals, is given in the Table (M denotes a molecule and M^+, M^- molecule-ions). The polarization energy was calculated on the assumption that M^+M^- constituted a dipole of length equal to the distance between neighbouring sites (5·23 Å, anthracene; 5·10 Å, naphthalene). To produce a pair of ions on neighbouring sites, 2·2 ev are needed for anthracene. To produce a widely separated pair of ions, wherein no coulombic attraction exists but the polarization of the crystal is greater by 1·2 ev than when the ions are neighbours, $2{\cdot}2 + 2{\cdot}8 - 1{\cdot}2 = 3{\cdot}8$ ev are necessary.

Compared with gaseous ionization, relatively little energy is required to ionize a molecule in a crystal or other condensed phase. Such a result must be of importance in the

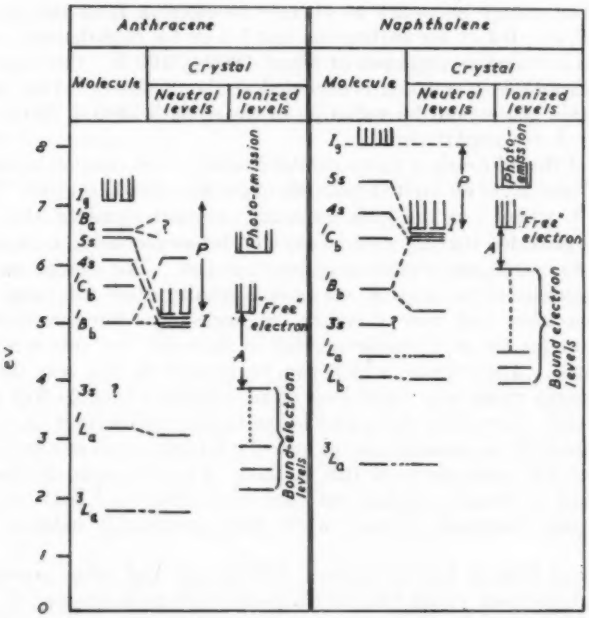
[6] Böttcher, "Theory of Electric Polarization," Elsevier, Amsterdam, 1952, p. 143.
[7] Mott and Gurney, "Electronic Processes in Ionic Crystals," Clarendon Press, Oxford, 1940.
[8] Gross and Karryev, *Doklady Akad. Nauk S.S.S.R.*, 1952, **84**, 471; Hayashi and Katsuki, *J. Phys. Soc. Japan*, 1952, **7**, 599; Pesteil and Zmerli, *Compt. rend.*, 1956, **242**, 2822.
[9] Lyons, *Nature*, 1950, **153**, 193.
[10] von Hippel, *Z. Physik*, 1936, **101**, 680.

photochemistry and even the thermochemistry of, for example, large aromatic molecules. The ionization of chlorophyll [11] is an example.

A summary of the results is given in Figs. 1 and 2, which show the energy levels observed and calculated as above. Only the lowest triplet level is shown. Rydberg levels for which $n = 3$ are omitted.

The probability of a transition from the ground state to an ionized level of a unit cell can be estimated as follows. Consider the transition of one electron from the highest

FIG. 1. *Anthracene.* FIG. 2. *Naphthalene.*



occupied molecular orbital f_α of molecule α to the lowest unoccupied orbital f_β' of the neighbouring molecule β. The transition moment $M = \int f_\alpha . \mathbf{r} . f_\beta' \, dv$ (where $\mathbf{r}$ is the co-ordinate of the electron). Since the orbitals are on different sites, $\mathbf{r}$ may be considered approximately constant; $\mathbf{r} \approx 5$ Å. Thus $M \approx 5 \int f_\alpha f_\beta' \, dv$ (Å). The integral, being the overlap of $2p\pi$ molecular orbitals, will be less than the overlap of two carbon $2p\pi$ orbitals, the axes of which are parallel when the centres are at the distance of closest approach of two carbon centres, one from each molecule in the crystal (3·5 Å). The overlap of two such atomic orbitals is *ca.* 0·008. Pairs of carbon centres separated by 5 Å or more will contribute almost nothing to the overlap of molecular orbitals, so that $\int f_\alpha f_\beta' \, dv < 10^{-3}$; and $M < 5 \times 10^{-3}$ Å. Hence the oscillator strength $f < 3 \times 10^{-5}$. We therefore conclude that $f \approx 10^{-5}$—10^{-6}, and transitions to ionic states are almost as weak as single–triplet transitions in molecules. A crystal between 1 and 10 mm. thick might therefore reveal absorption which produces ionized states, unless the bands are very diffuse. Such transitions bear an obvious resemblance to charge-transfer [12] spectra which,

[11] Calvin and Sogo, *Science*, 1957, **125**, 499.
[12] Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811.

however, are generally considered to arise from a partly ionic ground state. The lifetime of an ionized state should be at least 10^{-3} sec. and so fluorescence of this time constant would provide evidence for their existence. Observation of ionized states is therefore feasible. Have they been observed? In experimental spectroscopy the following observations may be relevant:

(*a*) In naphthalene crystals several mm. thick a band at 29,945 cm.$^{-1}$ has been repeatedly observed in both absorption and fluorescence at 20° K. It must mark an electronic transition. Previously it was suggested that it marks the second triplet level, but although the intensity seems rather high for this there is no certain conclusion possible at present. It could mark an ionized level.

(*b*) In both anthracene and naphthalene a phosphorescence lasting several minutes has been reported, with a maximum in both cases at *ca.* 5200 Å. The similarity of energy in the two cases means that ionised states are of doubtful relevance. The time constant also seems too long for what is being sought, so that ionised states are unlikely here, but not impossible.

Quantum-mechanical " mixing " of electronic states has so far not been considered, yet it certainly must occur. Mixing of the two lowest neutral exciton states has been both discussed and observed.[3] All ionized exciton states of the same crystal symmetry as neutral states must mix with them, with the result that the neutral states become partly ionic and *vice versa*. Ionic states of symmetry species B_u and A_u (in group C_{2h} of the unit cell) certainly exist and can be described in terms of molecular orbitals as $(1/\sqrt{2})(\phi_\alpha^+\phi_\beta^- \pm \phi_\alpha^-\phi_\beta^+)(\phi^+, \phi^-$ are of symmetries B_{3g}, B_{1u} in D_{2h}). The coefficients of mixing of such states with neutral states and with other ionized states can be determined, at least in principle, by use of second-order perturbation theory. Very roughly, the mixing will increase as the overlap increases and decrease with increasing energy separation of the states concerned. Since the overlap of $2p\pi$ neutral and ionized states is certain to be small, a " neutral " state will be only very slightly ionic. Thus the neglect of ionized states in earlier theories is justified. The physical effects of " mixing " will be seen, *e.g.*, in an increased probability of transition to an ionized state, as the result of its becoming partly neutral; if the coefficient were 10^{-4} the oscillator strength would increase in anthracene by 10^{-5}.

The more highly excited Rydberg states will overlap considerably with neighbouring orbitals of neighbouring molecules. The resulting mixing with ionic states would therefore be much greater than in the long-wavelength region of the spectrum. If mixing with a complete set of ionised states, $\sum_r X(\mathbf{K},\mathbf{r})$, occurs then the result can be expressed in an equivalent way for the excited electron in terms of a Bloch delocalized orbital (cf. ref. 13). Thus free-electron conductivity may arise in the more highly excited exciton states.

Ionized States and Photoconduction.—Free-electron ionized states, such as those above 5·1 ev in anthracene, should be photoconducting, with the greater fraction of the current carried by electrons. This photoconductivity has not yet definitely been observed, but there seems little doubt of its possibility.

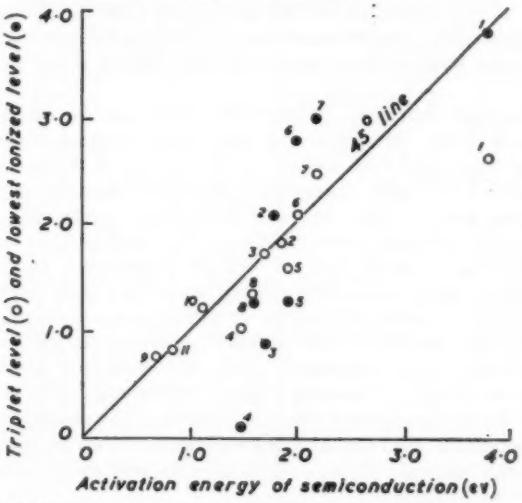
Light which is absorbed in a transition to a " neutral " exciton state may give rise to an ionized exciton state in two distinct ways: (*a*) directly, because the " neutral " state has a small probability of being ionized; and (*b*) indirectly, if a transition occurs from the " neutral " state to an ionized state of lower energy. In either case no current can flow under the influence of an electric field, since the positive and negative charges are bound in hydrogenoid orbitals and must move as a pair. Dissociation of the ion pair must occur. This could conceivably occur (i) at a suitable discontinuity in the lattice, (ii) thermally, or (iii) by a sufficiently strong electric fleld. The thermal energy necessary for dissociation from Figs. 1 and 2 is 0·5 ± 0·6 ev for anthracene and 0·8 ± 0·6 ev for naphthalene. The observed " activation energy " (derived from the temperature coefficient of the photocurrent) of photoconduction is 0·2 ev for anthracene. This mechanism therefore appears

[13] Slater and Shockley, *Phys. Rev.*, 1936, **50**, 705.

to be a real possibility. Strong electric fields must occur in the crystal (apart from the applied voltage) in the double layers on the surface and at the electrodes. (If the effect of oxygen and similar gases at the surface is indeed to form a more pronounced double layer than exists in a vacuum then a possible mechanism is obtained to explain the observed surface effect.) Both electric and thermal dissociation may therefore be expected. Fluorescence and phosphorescence processes of course compete with ionization mechanisms.

Ionised States and Semiconduction.— Fig. 3 shows the energy gap, ΔE, of semiconduction plotted against both the estimated height of the lowest ionized state and also the

FIG. 3. *Comparison of energy quantities.*



1, Naphthalene; 2, anthracene; 3, tetracene; 4, pentacene; 5, perylene; 6, pyrene; 7, chrysene; 8, anthanthrene; 9, pyranthrene; 10, ovalene; 11, violanthrene.

energy [14] of the molecular triplet level which can be assumed to resemble closely the value in the crystal. There appears to be some correlation, especially between the triplet level and the energy gap [defined by the equation $I = I_0 \exp(-\Delta E/2kT)$]. The experimental

Energy of formation of ionized states.

	Work needed (ev)	
	Anthracene	Naphthalene
Withdraw 2M from lattice	$2x$	$2y$
$M \longrightarrow M^+ + e^-$	7·2	8·1
$M + e^- \longrightarrow M^-$	−1·4	−0·7
Replace M^+ in lattice	$-x$	$-y$
Replace M^- in lattice, at a point distant from M^+	$-x$	$-y$
Bring M^+ and M^- to neighbouring sites	−2·8	−2·9
Polarize crystal surrounding ion pair	−0·8	−0·6
	2·2	3·9

and theoretical errors are both appreciable and any interpretation must therefore be cautious. It is not at all clear why a triplet level should need to be formed. The optical levels observed with pyranthrene, ovalene, and violanthrene have been assumed to be

[14] See Carswell, Ferguson, and Lyons, *Nature*, 1954, **173**, 736; Inokuchi, *Bull. Chem. Soc. Japan*, 1954, **27**, 22; 1956, **29**, 131; Northrop and Simpson, *Proc. Roy. Soc.*, 1956, *A*, **234**, 124; Mette and Pick, *Z. Physik*, 1953, **134**, 566.

triplets. A direct thermal equilibrium with dissociated ion pairs is expected and appears feasible in cases such as pentacene, perylene, and tetracene, although unlikely with pyrene and chrysene. Where the lowest ionized level lies above the triplet, formation of the latter is not sufficient to produce ions; some auxiliary and presumably non-thermal mechanism must be invoked. If a thermal mechanism operates then there is no reason for the triplet level to be indicated by the energy gap.

The author is grateful for the hospitality of the Department of Chemistry, Harvard University and, in particular, Professor William Moffitt; also to the U.S. Educational Foundation for a travel grant. Dr. W. G. Schneider is thanked for making available a manuscript before its publication, as is Dr. J. N. Murrell, who is independently considering the mixing of excitation waves in solid helium.

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1001. *The Chemistry of Silicon Carbide Surfaces.*

By S. G. CLARK and P. F. HOLT.

A layer exists on silicon carbide particles which dissolves more readily than the interior. The material of the layer exchanges with [^{31}Si]silicic acid. The surface of a silicon carbide particle appears to resemble that of a quartz particle.

SEVERAL methods have indicated that a layer exists on the surface of quartz particles which has a different composition from that of the interior, and was shown by Holt and King [1] to be silicic acid. Silicon carbide crystals normally have a surface layer which is not silicon carbide; Finch and Wilman,[2] by electron diffraction, estimated that its thickness was less than 43 Å. They believed it to be silica, formed by oxidation of the crystal surface in the furnace during manufacture. They could remove it by abrasion or hydrofluoric acid or aqueous alkali, and re-form it by heating the crystals in a Bunsen flame.

We have applied Holt and King's method [1] to the surface of a silicon carbide powder, prepared by grinding large crystals in a rubber-lined tumbling box through which air was drawn and separating the dust by elutriation. Particles of approximately 10 μ diameter were separated from this powder by sedimentation in water. The powders were prepared at room temperature and received no heat treatment except oven-drying at 120°. The specific area of the powder was measured both optically and by nitrogen adsorption (B.E.T. method), the latter giving the value 0·5 m.^{2}/g. and the former 0·14 m.^{2}/g. That the specific area of a quartz powder was determined by the B.E.T. method to be about four times the value obtained optically indicates that the surface roughness of the quartz and the silicon carbide were similar.

The silicon carbide powder was studied by following its rate of dissolution in dilute sodium hydroxide and by measuring the exchange of silicon when the particles were in contact with a solution of labelled orthosilicic acid.

Dissolution of Silicon Carbide in 0·1N-*Sodium Hydroxide.*—Silicon carbide powder (1 g.) and 0·1N-sodium hydroxide (15 ml.) were shaken gently in Polythene tubes at 25°. At measured intervals the tubes were opened and the suspensions centrifuged. A slight permanent turbidity was present in the supernatant liquid which increased with the time of extraction. The dissolved silica in the supernatant liquid was estimated colorimetrically; [3] under these conditions this silicomolybdate method gives a measurable change in colour intensity with a change in silica concentration of 0·015 mg. of SiO_2/100 ml.

The amount of dissolved silica increases rapidly during the first hour, then much more

[1] Holt and King, *J.*, 1955, 773.
[2] Finch and Wilman, *Trans. Faraday Soc.*, 1937, **23**, 337.
[3] King and Stantial. *Biochem. J.*, 1933, **27**, 990.

slowly (Fig. 1). After 10 hr. a linear plot is given, which, extrapolated to zero time, shows that 0·37 mg. of SiO_2 dissolves per g. of powder during the phase of rapid solution. The initial rapid dissolution indicates that there was a surface layer on the particles more readily soluble than the bulk.

Exchange between Dissolved [^{31}Si]*Silicic Acid and a Silicon Carbide Surface.*—Holt and King [1] showed that silicic acid exchanges between the surface layer on quartz and a solution in contact

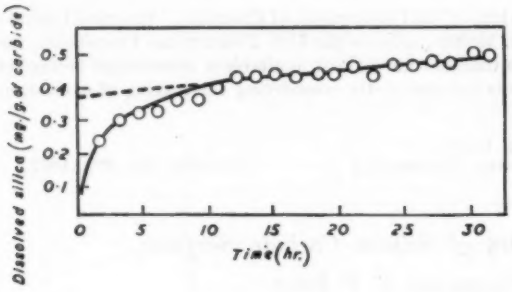
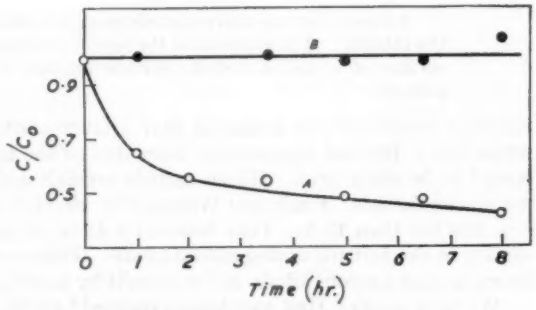


FIG. 1. *Rate of dissolution of silicon carbide powder in* 0·01N-*sodium hydroxide at* 25°.

FIG. 2. *Alteration in the concentration of* [^{31}Si]*silicic acid (curve A) and total silicic acid (curve B) on adding silicon carbide powder to a silicic acid solution at* pH 2·8. *The change in the concentration of the solute is denoted as the ratio of the concentration (C) after a measured time to the initial concentration* (C_0).



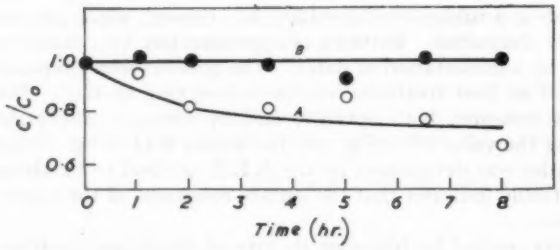


FIG. 3. *Alteration in the concentration of* [^{31}Si]*silicic acid (curve A) and total silicic acid (curve B) on adding silicon carbide powder to a silicic acid solution at* pH 8·7. *For C and* C_0 *see Fig.* 2.

with it. Evidence for a similar exchange between the layer on silicon carbide and dissolved silicic acid was sought.

Powdered fused silica (" Vitreosil ") was irradiated in the Harwell pile for 12 hr., then fused with sodium carbonate. A solution of the melt in water was brought to the required pH and diluted to 10 mg. of SiO_2 per 100 ml., whereat the solution is just below saturation with respect to orthosilicic acid and no polymerisation occurs.[4] Silicon carbide powder (1 g.) was gently shaken with this silicic acid solution (20 ml.) in Polythene tubes at 20°. Tubes were opened at intervals of up to 8 hr. and the contents filtered off. The total silica in the liquid was determined by the silicomolybdate colorimetric method and the labelled silica by a Geiger counter. Experiments were carried out in both acid and alkaline solutions. The solutions became increasingly turbid, particularly at alkaline pH, and more so if the silicon carbide had been pre-treated with sodium hydroxide

[4] Richardson and Waddams, *Research*, 1954, **7**, 542.

The results of the silica determinations are plotted in Figs. 2 and 3. The total mass of dissolved silica did not vary during the experiments but the mass of labelled dissolved silica fell rapidly at first, then more slowly until equilibrium was approached after 5—6 hr. Apparently, there is an exchange of silica between the surface of the silicon carbide powder and the solution. The constant value for the total dissolved silica precludes the possibility of the results' being due to adsorption.

Although Holt and King removed the layer from quartz by extraction with sodium hydroxide, after which treatment the dissolved silicic acid exchanged with surface silica at a diminished rate, we could not obtain a silicon carbide powder free from the rapidly-soluble layer by extraction with sodium hydroxide, washing with water, and air- or oven-drying. Possibly the rapidly-soluble layer is re-formed too quickly for the silicon carbide surface to be detected.

These results suggest that the surface of a silicon carbide particle is normally coated with a layer which resembles that on powdered quartz, whose formation does not require high temperatures. The extent of the layer on the powder can be estimated from the weight of silica which dissolves rapidly and the surface area of the powder, if it is assumed that the layer is silica. The volume, V, of a crystallographic unit cell is $M/N\rho$ (M, molecular weight; ρ, bulk density of the solid). The unit cell being assumed to be a cube, the area occupied by a cell in the surface is $V^{\frac{2}{3}}$. The weight of a monolayer covering 1 m.^{2} is $MV^{\frac{2}{3}}N^{-1} = 0{\cdot}89$ mg./m.^{2} ($M = 60$; $\rho = 2{\cdot}56$). The observed weight of the layer is 0·74 mg./m.^{2}. If the layer is hydrated, as is assumed, the area occupied would be somewhat larger, but data are not available for a calculation to be made. The readily soluble layer represents, approximately, a monolayer on the surface of the silicon carbide. (From the sensitivity of the silicomolybdate it is calculated that a change in silica concentration equivalent to one-hundredth of a monolayer could be detected.)

The rate of dissolution of the silicon carbide in dilute sodium hydroxide, calculated from the *linear* part of the curve, can be compared with the rates for quartz powders measured by King.[5] Two quartz powders gave the values 19 and 16 μg. of SiO_2/(m.^{2} hr.). After the powders had received prolonged treatment with sodium hydroxide to remove the outer layer, the rates were reduced to 8·8 and 10 μg. SiO_2/(m.^{2} hr.) respectively. The silicon carbide powder dissolved more rapidly [8 μg. of SiO_2/(m.^{2} hr.). The rate of dissolution of silicon carbide particles when the outer layer of silicic acid has been removed is, then, similar to that of the core of the quartz particles.

The fracture of silicon carbide crystals leaves in the newly-formed surfaces equal numbers of silicon and carbon atoms with unsatisfied valencies, and it must be supposed that reaction immediately occurs with either atmospheric oxygen or water vapour. If the silicon atoms react with oxygen, the surface must contain SiO ions; if, as is more likely, they react with water, the surface will consist of $Si(OH)_2$ ions. The outer layer of a silicon carbide particle will then resemble that of a quartz particle. In each case there is, apparently, adsorbed on this surface a layer of silicic acid. Dissolution of silicon carbide in dilute sodium hydroxide entails first the removal (rapid) of the adsorbed silicic acid and then the break-up of the main lattice, with the production of very small insoluble particles, possibly carbon, giving a turbid solution.

Elton and Mitchell [6] found that the ionic adsorption energies of various ions adsorbed on silicon carbide surfaces were remarkably similar to those when the ions were adsorbed on silica surfaces,[7] confirming our findings that the two surfaces are similar.

We thank the British Steel Castings Research Association for financial assistance and the Carborundum Company for gifts of crystalline silicon carbide.

THE UNIVERSITY, READING. [*Received, June 4th*, 1957.]

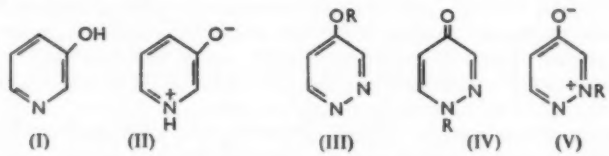
[5] King, M.Sc. Thesis, Reading, 1955.
[6] Elton and Mitchell, *J.*, 1947, 741.
[7] Benton and Elton, *Trans. Faraday Soc.*, 1953, **49**, 1213.

1002. *The Tautomerism of* N-*Heteroaromatic Hydroxy-compounds. Part II.* Ultraviolet Spectra.*

By S. F. Mason.

The ultraviolet spectra of a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives with fixed structures have been measured. By comparing spectra, it is found that tautomerism from O–H (*e.g.*, I) to N–H (*e.g.*, II) forms is general amongst the monoaza- and some diaza-heterocyclic hydroxy-compounds. Equilibrium constants (K_t = [N–H form]/[O–H form]) have been estimated from the spectra, and they have been found to increase with conjugation between the oxygen and the nitrogen atom, and with the addition of fused benzene rings, and to decrease with aza-substitution, with a rise in temperature, and with a fall in the dielectric constant of the solvent.

The ultraviolet spectra of a number of heteroaromatic compounds with a hydroxyl group α or γ to a ring-nitrogen atom have been shown to resemble those of the corresponding *N*-methyl derivatives and to differ from those of the corresponding *O*-methyl derivatives, in alcohol or aqueous solution, establishing that these compounds tautomerise predominantly to amide forms.[1] Other *N*-heteroaromatic hydroxy-compounds have been less extensively studied. From the ultraviolet spectra in alcohol and in aqueous solutions of arbitrary pH, it has been concluded that the hydroxy-quinolines and *-iso*quinolines with a hydroxyl group neither α nor γ to a ring-nitrogen atom are essentially phenolic.[2] However, 2- and 4-hydroxyacridine [3] and 2-hydroxyphenazine,[4,5] on passing from non-aqueous to aqueous-alcohol or water solutions, undergo marked spectral changes which have been attributed to tautomerism from O–H to N–H forms,[3,4,5] and 3-hydroxypyridine has been shown by ultraviolet spectroscopy to exist equally as enol (I) and zwitterionic (II) forms in neutral aqueous solution.[6]



(I) (II) (III) (IV) (V)

In the present work the ultraviolet spectra of a wide range of *N*-heteroaromatic hydroxy-compounds have been examined in organic solvents and in aqueous solutions buffered to the isoelectric pH values of the compounds. For comparison, the spectra of the corresponding *N*-methyl and, where available, the *O*-methyl derivatives have been measured. The results show (Table 1) that the compounds with a hydroxyl group α or γ to a ring-nitrogen atom have a spectrum similar to that of their *N*-methyl derivative and different from that of their *O*-methyl derivative both in organic and in aqueous solvents, indicating that they tautomerise predominantly to the amide form under these conditions. The diaza-compounds with one nitrogen atom α or γ to the hydroxyl group and the other in a non-conjugated position may tautomerise from an enol (*e.g.*, III; R = H) to an amide (*e.g.*, IV; R = H) or a zwitterion (*e.g.*, V; R = H) form. In these cases too the amide

* Part I, *J.*, 1957, 4874.

[1] Specker and Gawrosch, *Ber.*, 1942, **75**, 1338; Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923; Hearn, Morton, and Simpson, *J.*, 1951, 3318; Brown, Hoerger, and Mason, *J.*, 1955, 211; Brown, and Mason, *J.*, 1956, 3443; Den Hertog and Buurman, *Rec. Trav. chim.*, 1956, **75**, 257.

[2] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

[3] Albert and Short, *J.*, 1945, 760.

[4] Badger, Pearce, and Petit, *J.*, 1951, 3204.

[5] Perkampus, *Z. phys. Chem.* (*Frankfurt*), 1956, **6**, 18.

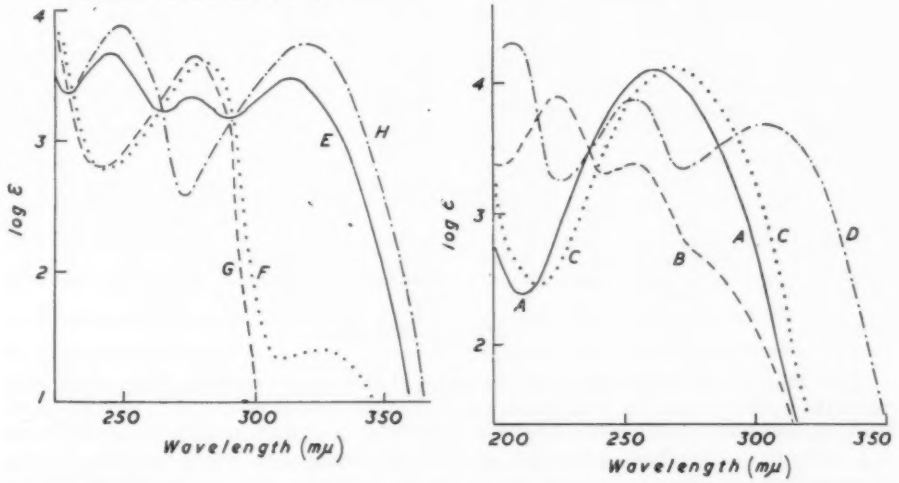
[6] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.

form is preferred, as the spectrum of 4-hydroxypyridazine resembles that of its 1-methyl (IV; R = Me) but not that of its 2-methyl (V; R = Me) or its *O*-methyl (III; R = Me) derivative (Fig. 1, Table 1).

The monoaza- and some diaza-compounds with a hydroxyl group neither α nor γ to a ring-nitrogen atom show a change of spectrum on passage from an organic solvent to an aqueous solution at the isoelectric pH (Fig. 2, Table 1). The spectrum of a given compound in alcohol solution resembles closely that of the *O*-methyl derivative, but in aqueous solution new bands appear with positions corresponding to those observed in the spectrum of the *N*-methyl derivative. A continuous change of spectrum with solvent composition is observed in alcohol–water and dioxan–water mixtures, the bands in the same positions

FIG. 1. *Absorption spectra of* (*A*) 4-*hydroxypyridazine* (*neutral molecule*) (pH 4·8), (*B*) 4-*methoxypyridazine* (*neutral molecule*) (pH 7·0), (*C*) 1-*methyl*-4-*pyridazone* (*neutral molecule*), *and* (*D*) 4-*hydroxypyridazine* 2-*methochloride* (*zwitterion*) (pH 7·0).

FIG. 2a. *Absorption spectra of* (*E*) 3-*hydroxypyridine in aqueous buffer* (pH 6·90), (*F*) 3-*hydroxypyridine in alcohol*, (*G*) 3-*methoxypyridine* (*neutral molecule*), *and* (*H*) 3-*hydroxypyridine methochloride* (*zwitterion*) (pH 7·0).

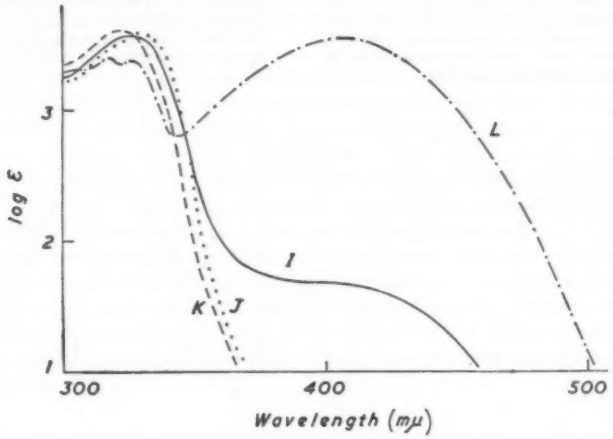


as those of the *N*-methyl derivative falling, and those at the same wavelength as the bands of the *O*-methyl derivative rising, in intensity as the dielectric constant decreases. The absorption curves in such mixtures show a single set of isosbestic points, indicating that the spectral changes are due to the displacement of a single equilibrium process with change of solvent. In general, therefore, both enol (*e.g.*, I and VI) and zwitterionic (*e.g.*, II and VII) forms exist in equilibrium in solvents of high dielectric constant.

The *N*-methyl derivative of a given compound invariably absorbs radiation at a longer wavelength than the *O*-methyl derivative (Fig. 2, Table 1), and a particular feature of the change of spectrum with solvent shown by the parent hydroxy-compound is the appearance of a band in aqueous solution beyond the long-wavelength limit of absorption in alcohol solution. The intensity of this band, which is due to the absorption of the zwitterionic form alone, thus affords a measure of the tautomeric equilibrium. Methyl groups, for the most part, exert only second-order effects on the position and intensity of allowed electronic transitions ($\varepsilon > 1000$), and accordingly the spectrum of an *N*-methyl derivative may be taken as a good model for the absorption characteristics of the zwitterionic tautomer of the parent hydroxy-compound. On this assumption the relative amounts of the enol and zwitterionic forms of a given *N*-heteroaromatic hydroxy-compound at the isoelectric pH may be calculated from the intensities of the bands of longest wavelength in the spectra

of the compound and its *N*-methyl derivative. Values of the calculated tautomeric equilibrium constants (K_t = [N–H form]/[O–H form]) are listed in Table 1. In some diaza- and some tricyclic cases the spectra of the corresponding *N*-methyl derivatives were not available. However, the spectra of analogous monoaza- or dicyclic *N*-methyl derivatives allow lower or upper limits respectively to be calculated for K_t, as the intensity of the long-wavelength band in the spectrum of a given *N*-methyl compound, in general, decreases on aza-substitution and increases with the addition of a fused benzene ring (cf. compounds 6, 16, 22, 33, and 44; 29 and 60; 24 and 64; Table 1).

FIG. 2*b*. *Absorption spectra of* (*I*) 6-*hydroxyquinoline in aqueous buffer* (pH 7·02), (*J*) 6-*hydroxyquinoline in alcohol*, (*K*) 6-*methoxyquinoline* (*neutral molecule*) (pH 7·5), *and* (*L*) 6-*hydroxyquinoline methochloride* (*zwitterion*) (pH 10).



The value of K_t varies widely in the range of compounds studied, being often large when the hydroxyl group is conjugated with a ring nitrogen atom or is β to such an atom. Conjugation allows dipolar resonance forms (*e.g.*, VIa) to contribute with the neutral form (*e.g.*, VIb) to the structure of the enol, and neutral transannular amide forms (*e.g.*, VIIa) to contribute with the dipolar form (*e.g.*, VIIb) to the structure of the zwitterion. These types of resonance may be expected to favour the N–H tautomer at the expense of the O–H tautomer. The values for K_t show that transannular "*para-para*-quinonoid" structures (*e.g.*, VIII) are more effective in this respect than "*ortho-para*-quinonoid" structures (*e.g.*, VIIa), which in turn are more effective than "*ortho-ortho*-quinonoid" structures (*e.g.*, IX). The addition of a fused benzene ring to a compound with a given type of conjugation usually enhances K_t (cf. compounds 23 and 63; 28 and 59), presumably because the entire benzenoid resonance is replaced by quinonoid resonance in the dicyclic cases (*e.g.*, VIIa), whilst only two-thirds of the benzenoid resonance is so replaced in the corresponding tricyclic cases (*e.g.*, X). 2-Hydroxyphenanthridine has a lower K_t value than its dicyclic analogue, 7-hydroxyquinoline, but here the benzenoid resonance of all three rings must be replaced by quinonoid resonance in the transannular amide form (XI).

The β-hydroxy-compounds, 3-hydroxypyridine and 4-hydroxy*iso*quinoline, but not 3-hydroxyquinoline, possess much larger K_t values than any other compound in which the nitrogen and oxygen atoms are not conjugated (Table 1). In such compounds the carbon atoms vicinal to the ring-nitrogen atom are conjugated to the oxygen atom, and their electronegativity is greatly enhanced by the adjacent positively charged nitrogen atom in the zwitterionic N–H tautomer. Thus *o*- and *p*-quinonoid structures with negative

TABLE 1. *The absorption spectra of* N*-heterocyclic hydroxy-compounds and their* O- *and* N*-methyl derivatives in the visible and ultraviolet regions, and the values of their tautomeric constants,* K_t = [Zwitterion]/[Enol], *calculated from the spectra.* (*Wavelengths and molecular extinctions in italics refer to shoulders or inflexions.*)

No.	Compound	pK_a (H_2O; 20°)	Solvent [a]	$\lambda_{max.}$ (mμ)	ε	K_t
1	2-Hydroxypyridine	0·75 [c]; 11·62 [c]	pH 6, CH	293; 224 298; 230	5890; 7230 4540; 8880	*h*
2	2-Methoxypyridine	3·28 [c]	pH 7	269	3230	
3	1-Methyl-2-pyridone	0·32 [c]	pH 5	297; 226	5700; 6100	
4	3-Hydroxypyridine	4·86 [c]; 8·72 [c]	pH 6·80 EtOH	315; 278; 246; 211 279; 215	3060; 2320; 5120; 15,800 4440; 6480	1·27
5	3-Methoxypyridine	4·88 [c]	pH 7·0	276; 216	3960; 8320	
6	3-Hydroxypyridine methochloride	4·96 [c]	pH 7·0	320; 249; 213	5810; 8120; 24,640	
7	2-Hydroxypyrazine	−0·1 [c]; 8·23 [c]	pH 4·5 EtOH	317; 221 321; 224	5520; 8820 5490; 8950	*h*
8	2-Methoxypyrazine	0·75 [c]	pH 7·0	290; 209	5240; 9600	
9	1-Methyl-2-pyrazone	−0·04 [c]	pH 7·0	323; 223	5610; 9370	
10	3-Hydroxypyridazine	−1·8 [c]; 10·46 [c]	pH 6·0 EtOH	281; 220 290; 222	2790; 3160 2700; 3600	*h*
11	3-Methoxypyridazine	2·52 [c]	pH 6·0	265	2330	
12	2-Methyl-3-pyridazone [b]	— [c]	EtOH	295; 223	3100; 3100	
13	4-Hydroxypyridazine	1·07 [c]; 8·68 [c]	pH 4·8 EtOH	262 266	12,740 13,100	*h*
14	4-Methoxypyridazine	3·70 [c]	pH 7·0	254; 224	2570; 8240	
15	1-Methyl-4-pyridazone [b]	—	EtOH	269	14,800	
16	4-Hydroxypyridazine 2-methochloride	1·74 [d]	pH 7·0	302; 254; 207	4840; 8240; 22,120	
17	5-Hydroxypyrimidine	1·87 [d]; 6·78 [d]	pH 4·32 EtOH	*325*; 271; 214 276; 218	107; 4750; 9720 5330; 9970	⩾0·02 [1]
18	2-Hydroxyquinoline	−0·31 [c]; 11·74 [c]	pH 5·5	324; 270; 245; 224	6300; 6550; 8520; 26,720	*h*
19	2-Methoxyquinoline	3·17 [c]	pH 6·8	318; 307; 267; *260*	2200; 2070; 2000; *1990*	
20	1-Methyl-2-quinolone	−0·71 [c]	pH 7·0	325; 272; 245; 228	6500; 6900; 10,250; 34,100	
21	3-Hydroxyquinoline	4·30 [c]; 8·06 [c]	pH 6·18 EtOH	365; 330 + 321; *270* 334 + 324; 278 + 267	430; 4080 + 4100; *3060* 4800 + 4850; 3000 + 3080	0·064
22	3-Hydroxyquinoline methochloride	5·42 [d]	pH 10	384; 320 + 308; 255	7140; 1700 + 1680; 14,600	
23	5-Hydroxyquinoline	5·20 [c]; 8·54 [c]	pH 6·87 EtOH	450; 312; *268*; 240 323; 242	193; 2870; *3290*; 37,400 3400; 56,000	0·054
24	5-Hydroxyquinoline methochloride	6·12 [d]	pH 8·5	462; 332 + 318; 273	3800; 1150 + 1240; 33,100	
25	6-Hydroxyquinoline	5·17 [c]; 8·88 [c]	pH 7·02 EtOH	*400*; 325; 272; 225 331; 274; 227	*49*; 3860; 3060; 30,500 4100; 2800; 32,100	0·014
26	6-Methoxyquinoline	5·06 [d]	pH 7·5	325; 268; 223	3900; 2940; 32,400	
27	6-Hydroxyquinoline methochloride	7·15 [d]	pH 10	408; 325 + 316; 270	3500; 3950 + 4000; 26,800	
28	7-Hydroxyquinoline	5·48 [c]; 8·85 [c]	pH 7·16 EtOH	402; 327; 258; 225 333; 263; 227	3030; 3810; 12,800; 26,700 5250; 2910; 37,400	0·43
29	7-Hydroxyquinoline methochloride	5·56 [d]	pH 8	406; 311; 261	10,000; 1550; 32,500	
30	8-Hydroxyquinoline	5·13 [c]; 9·89 [c]	pH 7·51 EtOH	430; 303; *270*; 240 305; 242	51; 2100; *2290*; 17,200	0·035
31	8-Hydroxyquinoline methochloride	6·81 [d]	pH 10	442; 346 + 334; 273	1520; 1310 + 1200; 37,000	
32	4-Hydroxy*iso*quinoline	4·80 [d]; 8·68 [d]	pH 6·74 EtOH	359; *320*; *240* 330; 295; 230	7640; *4260*; 8800 4860; 3950; 16,100	3·76
33	4-Hydroxy*iso*quinoline methochloride	4·93 [d]	pH 8·5	364; *320*; 248	9660; 3670; 9180	

TABLE 1. (*Continued.*)

No.	Compound	pK_a (H_2O; 20°)	Solvent [a]	$\lambda_{max.}$ (mμ)	ε	K_t
34	5-Hydroxy*iso*quinoline	5·40 [d]; 8·45 [d]	pH 6·92	*400*; 330; 296; 230	*135*; 4400; 3570; 22,800	0·038
			EtOH	326; 302; 235	5200; 5260; 30,600	
35	5-Hydroxy*iso*quinoline methochloride	6·90 [d]	pH 10·0	408; 349; 269; 233	3720; 6120; 21,000; 16,800	
36	6-Hydroxy*iso*quinoline	5·85 [d]; 9·15 [d]	pH 7·50	353; 263; 229	8040; 17,200; 43,600	1·92
			CH	319; 280; 225	694; 2160; 25,600	
37	6-Hydroxy*iso*quinoline methochloride	6·02 [d]	pH 10·0	358; 267; 230	12,220; 22,900, 34,400	
38	7-Hydroxy*iso*quinoline	5·70 [d]; 8·88 [d]	pH 7·29	400; 338; 257; 221	*110*; 3060; 6550; 49,000	0·038
			EtOH	338; 259; 225	3460; 5510; 52,500	
39	7-Hydroxy*iso*quinoline methochloride	7·09 [d]	pH 10·0	408; 298; 261	2970; 8200; 50,400	
40	8-Hydroxy*iso*quinoline	5·66 [d]; 8·40 [d]	pH 7·03	430; 328; *247*	2700; 4340; *15,500*	0·87
			EtOH	380; 333; 233	1860; 4050; 28,000	
41	8-Hydroxy*iso*quinoline methochloride	5·81 [d]	pH 10·0	400; 334; 257	5820; 4950; 20,000	
42	4-Hydroxy-1 : 5-naphthyridine	2·85 [e]; 10·01 [e]	pH 6·5	323; 240	9600; 25,120	*h*
			EtOH	328; 242	9370; 26,300	
43	8-Hydroxy-1 : 6-naphthyridine	4·08 [e]; 8·33 [e]	pH 6·20	368; 325; 257; 239	2160; 3110; 12,000; 14,480	0·90
			EtOH	327; 241	3700; 27,920	
44	8-Hydroxy-1 : 6-naphthyridine 6-methochloride	4·34 [e]	pH 7·0	362; 260	4550; 9600	
45	8-Hydroxy-1 : 7-naphthyridine	2·64 [e]; 12·01 [e]	pH 7·32	325; 283; 239	3470; 5620; 12,080	*h*
			EtOH	331; 285; 240	3440; 5670; 13,100	
46	5-Hydroxycinnoline	1·92 [f]; 7·40 [f]	pH 4·66	356; *305*; 244	2480; *1190*; 32,480	*h*
			EtOH	359; *305*; 245	2430; *1200*; 33,100	
47	6-Hydroxycinnoline	3·65 [f]; 7·52 [f]	pH 5·58	402; 320; 281; 238	1200; 4720; 3750; 24,000	⩾0·1 [m]
			EtOH	326; 241	4850; 40,500	
48	7-Hydroxycinnoline	3·31 [f]; 7·56 [f]	pH 5·44	448; 354; 267; 235	282; 2970; 5140; 42,600	⩾0·03 [m]
			EtOH	355; *275*; 237	3970; *6100*; 47,600	
49	8-Hydroxycinnoline	2·74 [e]; 8·20 [e]	pH 5·47	525; 359; 296; 242	21; 2610; 1240; 32,200	⩾0·004
			EtOH	362; 303; 246	2700; 1110; 34,000	
50	6-Hydroxyphthalazine	3·94 [d]; 7·95 [d]	pH 5·95	*375*; 325 + 313; 275	*1540*; 3070 + 3110; 5950	⩾0·1 [m]
			EtOH	317; 279; 228	3140; 6680; 38,200	
51	6-Hydroxyquinazoline	3·12 [e]; 8·19 [e]	pH 5·65	336; 264; 231	3270; 3290; 31,600	*h*
			EtOH	342; 265; 233	3700; 3690; 45,000	
52	8-Hydroxyquinazoline	3·41 [e]; 8·65 [e]	pH 6·03	324; 239	2550; 28,080	*h*
			EtOH	329; 241	2670; 29,100	
53	8-Hydroxyquinazoline 3-methochloride	7·26 [e]	pH 10·5	443; 328 + 317; 275	174; 5150 + 5470; 6210	
54	5-Hydroxyquinoxaline	0·9 [e]; 8·65 [e]	pH ·380	*355*; 325; 250	*1460*; 2860; 30,280	*h*
			EtOH	*363*; 326; 252	*1520*; 2900; 30,000	
55	5-Hydroxyquinoxaline 1-methochloride	5·74 [e]	pH 10	550; 335; 288; 237	2440; 1780; 28,400; 9100	
56	6-Hydroxyquinoxaline	1·40 [e]; 7·92 [e]	pH 4·66	342; 244	5880; 20,400	*h*
			EtOH	350; 245	5950; 21,000	
57	1-Hydroxyacridine	4·18 [g]; 10·7 [g]	10% EtOH–H_2O	*550*; 386; 358	*42*; 3450; 3670	0·036
			EtOH [h]	392; 360	3550; 3550	
58	1-Hydroxyacridine methochloride	—	pH 9—10 [i]	550; 380	1200; 3600	
59	2-Hydroxyacridine	4·86 [g]; 9·9 [g]	20% EtOH–H_2O [h]	466; 363; 351	10,000; 16,000; 12,500	2·5
			90% Et_2O–EtOH [h]	391; 351	5600; 8000	
60	2-Hydroxyacridine methochloride	—	pH 9—10 [i]	470; 350	14,000; 12,000	
61	3-Hydroxyacridine	5·52 [e]; 8·81 [e]	10% EtOH–H_2O	*500*; 380; 355	*60*; 4470; 6300	0·015
			EtOH [h]	396; 354	5000; 7000	

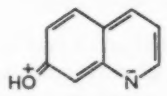
TABLE 1. (*Continued.*)

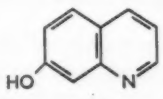
No.	Compound	pK_a (H_2O; 20°)	Solvent *	$\lambda_{max.}$ (mμ)	ε	K_t
62	3-Hydroxyacridine methochloride	—	pH 9—10 [f]	500; 370	4000; 10,000	
63	4-Hydroxyacridine	4·45 [e]; 9·4 [g]	20% EtOH–H_2O [h]	570; 398; 360	1000; 2800; 5000	0·33
			EtOH [h]	400; 358	2800; 4500	
64	4-Hydroxyacridine methochloride	—	pH 9—10 [f]	570; 360	4000; 4500	
65	2-Hydroxyphenanthridine	4·82 [e]; 8·79 [e]	pH 6·80	*450*; 360 + 347; 253	*17*; 2270 + 2240; 45,200	⩽0·001 [n]
			EtOH	365 + 351; 254	2400 + 2460; 43,600	
66	6-Hydroxyphenanthridine	5·35 [e]; 8·43 [e]	pH 6·89	377; 328; 299; 251	10,400; 3500; 8000; 43,600	⩽5 [n]
			Dioxan	328; 297; 254	1360; 13,600; 50,000	
67	7-Hydroxyphenanthridine	4·39 [d]; 8·68 [d]	10% EtOH–H_2O	*395*; 361 + 347; 301	*315*; 2300 + 2310; 4680	⩽0·1 [q]
			EtOH	364 + 349; 303; 253	2550 + 2510; 4060; 44,100	
68	2-Hydroxyphenazine	2·6 [e]; 7·5 [e]	H_2O [j]	490; 410; 365	2800; 4200; 9000	⩾0·25 [r]
			EtOH [j]	410; 355	6500; 9000	

* H_2O unless otherwise stated; CH = *cyclo*hexane.

[a] Quoted from Druey, Eichenberger, and Rometsch, *Helv. Chim. Acta*, 1954, **37**, 1298. [b] Unpublished values kindly provided by Drs. J. Druey and P. Schmidt. [c] pK_a values quoted from Albert and Phillips, *J.*, 1956, 1294. [d] pK_a values quoted from Part III. [e] pK_a values quoted from Albert and Hampton, *J.*, 1954, 505. [f] pK_a values quoted from Osborn and Schofield, *J.*, 1956, 4207. [g] pK_a values for 50% alcohol quoted from Albert, "The Acridines," Arnold, London, 1951, p. 114. [h] Spectra quoted from Albert and Short, *J.*, 1945, 760. [i] Spectra quoted from Nitzsche, *Ber.*, 1944, **77**, 337. [j] Spectra quoted from Badger, Pearce, and Petit, *J.*, 1951, 3204. [k] Not measurable spectroscopically. [l] Based on the extinction of the 320 mμ band of compound 6. [m] Based on the extinction of the 358 mμ band of compound 37. [n] Based on the extinction of the 406 mμ band of compound 29. [p] Based on the extinction of the 440 mμ band of compound 41. [q] Based on the extinction of the 408 mμ band of compound 39. [r] Based on the extinction of the 470 mμ band of compound 60.

charge on one or the other of the vicinal carbon atoms (*e.g.*, XII, XIII, and XIV) should make relatively important contributions to the stability of the N–H tautomer in these cases. The effectiveness of the structures may be expected to have the order (XIV) > (XII) > (XIII), for in (XIII) the benzenoid resonance of both rings is replaced by quinonoid resonance, whilst in (XIV) the benzenoid resonance of only one ring is lost.


(VIa)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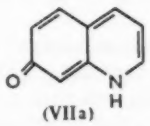
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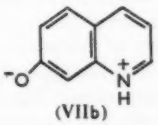
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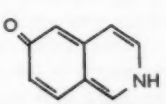
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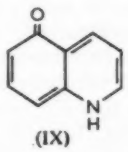
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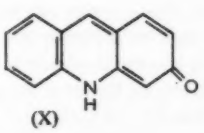
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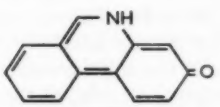
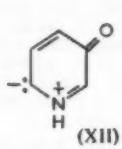
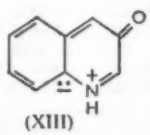

(XI)

Thus the K_t value of 4-hydroxy*iso*quinoline is larger than that of 3-hydroxypyridine, whilst that of 3-hydroxyquinoline is smaller (Table 1). The K_t values of the other hydroxy-quinolines and -*iso*quinolines in which the nitrogen and oxygen atoms are not formally conjugated are of the same magnitude as that of 3-hydroxyquinoline (Table 1), and in these compounds too the benzenoid resonance of both aromatic rings is replaced by quinonoid resonance in the structure analogous to (XIII) contributing to the resonance hybrid of the zwitterionic N–H tautomer.

The diaza-compounds have smaller K_t values than their monoaza-analogues (Table 1), since a second nuclear nitrogen atom reduces the proton-accepting property of the first more than it enhances the proton-releasing property of the oxygen atom. Thus the ionisation constants of 4-hydroxy*iso*quinoline are separated by 3·88 pK_a units, whilst those of 8-hydroxy-1 : 6-naphthyridine are separated by 4·25 units, and the tautomeric constant of the former compound is four times as large as that of the latter. In the latter compound, where the two nitrogen atoms are substituted in different rings, the decrease in K_t is smaller than in the cases (compounds 46—49, Table 1) where they are substituted in the same ring. The proton-accepting capacity of a nitrogen atom is lowered more by another nitrogen atom substituted in the same ring than in the condensed ring (Table 1), as such an atom reduces the π-electron density of the ring in which it is substituted more than that of the condensed ring.[7]


(XII)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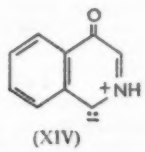
(XIV)

7-Hydroxycinnoline has a larger K_t value than the 8-isomer, yet their zwitterionic forms may both resonate with neutral "*ortho-para*-quinonoid" amide forms; among their monoaza-analogues, 7-hydroxyquinoline and 8-hydroxy*iso*quinoline have K_t values of the same order (Table 1). In 8-hydroxycinnoline intramolecular hydrogen-bonding favours the enol tautomer, as a zwitterion stabilised by resonance with a neutral form requires the breaking of the hydrogen bond and the union of the tautomeric proton with the 2-nitrogen atom. In 8-hydroxyquinoline, on the other hand, intramolecular hydrogen-bonding favours the zwitterion form, as its K_t value is larger than that of the 6-isomer, whilst 5- and 7-hydroxy*iso*quinoline, which are analogous in that the hydroxyl group is not substituted in the same ring as the nitrogen atom and is not conjugated to it, have the same K_t values (Table 1). Thus $^+$N–H···O$^-$ hydrogen-bonding is stronger than comparable O–H···N bonding. The standard free-energy change of the tautomeric equilibrium at 20° is 500 cal. larger in 8- than in 6-hydroxyquinoline, and the strengths of these types of hydrogen bond differ to approximately the same degree if the standard entropy changes of the two equilibria are similar.

The tautomerism of *N*-heteroaromatic hydroxy-compounds to zwitterionic forms is repressed in solvents of low dielectric constant. The variation of the classical tautomeric constant of 6-hydroxy*iso*quinoline with dielectric constant has been determined from the molar extinction of the 353 mμ band of this compound in dioxan–water mixtures of varied compositions at 20°. The constant falls by a factor of 800 as the dielectric constant is reduced from 80 to 2·1 (Table 2), and since the activity coefficient of the neutral enol form is probably not greatly affected by a change of solvent, the fall must be due principally to an increase in the activity coefficient of the zwitterionic N–H form with the decrease in dielectric constant. A plot of the logarithm of the tautomeric constant (log K_t) against the logarithm of the dielectric constant (log D) does not give a straight line (Table 2), the curve obtained suggesting that log K_t is proportional to $D^{0\cdot3}$ in the region of high dielectric constant and to $D^{0\cdot7}$ in the region of low dielectric constant.

An increase in temperature also represses the tautomerism of *N*-heteroaromatic hydroxy-compounds to zwitterionic forms, showing that the tautomerism is exothermic. The thermal variation of the tautomeric constants of four compounds, representing the type of no conjugation and the three types of transannular *o*- and *p*-quinonoid conjugation between the nitrogen and the oxygen atom, have been measured from the change of their

[7] Coulson and Longuet-Higgins, *J.*, 1949, 971.

absorption spectra with temperature over the range 15—85°. From the observed constants, the standard heat content and entropy changes of the tautomerism at 20° and 80° have been calculated (Table 3), the values obtained being accurate to within about 10%. The results (Table 3) show that, at a given temperature, the variation of the change in standard free energy of tautomerism from compound to compound is due mainly to the

TABLE 2. *The tautomeric equilibrium constant* (K_t = [N–H form]/[O–H form]) *of 6-hydroxyisoquinoline in dioxan–water at* 20°.

Dioxan (%) ...	0	10	20	30	40	50	60	70	80	90	100
Dielectric constant *	80	71	62	53	44	32	27	18	11	5·7	2·1
log K_t	0·29	0·11	−0·15	−0·38	−0·66	−0·93	−0·98	−1·26	−1·59	−2·01	−2·62

* Quoted from Åkerlof and Short, *J. Amer. Chem. Soc.*, 1936, **58**, 1241.

variation of the heat-content change. The standard entropy change of the tautomerism, at a given temperature, is approximately constant for 3-hydroxypyridine and 6- and 8-hydroxy*iso*quinoline, though not for 5-hydroxyquinoline. The anomalous entropy change in the tautomerism of 5-hydroxyquinoline cannot be due to the steric effect of a C–H group *peri* to the hydroxyl group, as the hydroxyl group in 8-hydroxy*iso*quinoline is also *peri* to a C–H group. The most important factor contributing to the standard entropy change of the tautomerism of a *N*-heteroaromatic hydroxy-compound may be expected to be the increase in order resulting from the solvation of the zwitterion. The solvation of a zwitterion at a given temperature, and the decrease of that solvation with an increase in temperature, are not likely to vary widely from one compound to another in the present series, so that an approximately constant standard entropy change of tautomerism is to be expected at a given temperature for the compounds studied.

TABLE 3. *Variation of the tautomeric equilibrium constant* (K_t = [N–H form]/[O–H form]) *with temperature, and the standard heat content* (ΔH) *and entropy* (ΔS) *changes at* 20° *and* 80°.

	log K_t				$-\Delta H$ (kcal./mole)		$-\Delta S$ (cal./mole/°c)	
	20°	40°	60°	80°	20°	80°	20°	80°
6-Hydroxy*iso*quinoline ...	0·29	0·16	0·03	−0·16	2·6	6·0	7·3	17·7
3-Hydroxypyridine	0·10	−0·05	−0·22	−0·40	2·5	5·7	7·8	17·9
8-Hydroxy*iso*quinoline ...	−0·06	−0·17	−0·30	−0·50	2·1	5·3	7·5	17·3
5-Hydroxyquinoline	−1·28	−1·36	−1·44	−1·54	1·6	3·0	11·0	15·6

EXPERIMENTAL

Sources of Materials.—These were as in Part I (preceding paper).

Absorption Spectra.—These were measured with a Hilger Uvispek H700/305 quartz spectrophotometer, in the solvent listed in Table 1. The buffer solutions were 0·01M-acetate (for pH 3·8—5·7), 0·01M-phosphate (for pH 6·0—7·9, and 10·3—11·3), and 0·01M-borate (for pH 8·2—10·0). The variations of the spectra with temperature were measured by means of a water-jacketed cell-holder maintained at a constant temperature (±0·05°) with water circulated from a thermostat.

The author thanks Professor A. Albert for helpful discussion, Mr. D. Light for technical assistance, and the Australian National University for a Research Fellowship.

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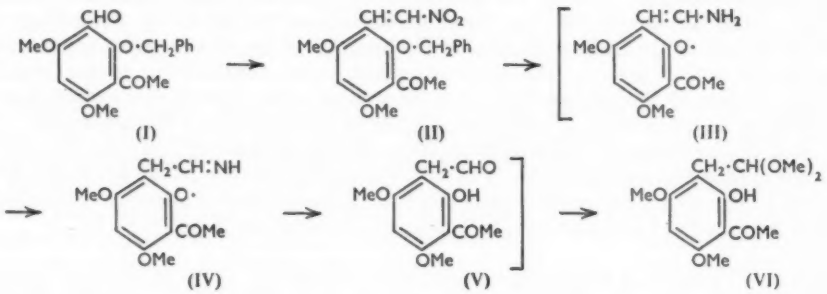
1003. *Vitexin. Part II.*[1] *The Synthesis of 3-Acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde Dimethyl Acetal.*

By Alexander Robertson and W. R. N. Williamson.

The structure of the degradation product of dehydrodi-*O*-methyl*secoapo*vitexin, believed to be 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde dimethyl acetal,[1] has been confirmed by its synthesis from 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone by way of 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene.

By the action of hot methanolic sulphuric acid dehydrodi-*O*-methyl*secoapo*vitexin [1] gave rise to pyruvaldehyde and an optically inactive compound $C_{10}H_8O_2(OMe)_4$ which from its properties was considered to be the dimethyl acetal (VI) of 3-acetyl-2-hydroxy-4 : 6-dimethylphenylacetaldehyde. This conclusion has been confirmed by a rational synthesis of the compound identical with the natural derivative.



Interaction of 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (I) with nitromethane in pyridine containing a little piperidine gave 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene (II) which on reduction with iron and acetic acid [2] in alcohol followed by heating of the resulting crude amine (III) with methanolic sulphuric acid, with simultaneous removal of the benzyl group, furnished the dimethyl acetal (VI) by way of the stages (IV) and (V).

In some exploratory experiments 3-acetyl-2-benzyloxy-4 : 6-dimethoxycinnamic acid was prepared but attempts to hydroxylate this gave only traces of an acidic substance. Reduction of 2-benzyloxy-ω : 4 : 6-trimethoxyacetophenone with lithium aluminium hydride, potassium borohydride, or aluminium amalgam furnished products inconsistent with the simple reduction of the carbonyl group.

Experimental

The infrared absorption spectra were determined in a Nujol mull with a Perkin-Elmer model 21 double-beam spectrophotometer.

2-Benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (I).—A mixture of 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone [1] (1·27 g.), potassium carbonate (2·5 g.), benzyl bromide (5 ml.), a trace of potassium iodide, and acetone (50 ml.) was heated under reflux for 13 hr. On isolation the resulting *benzyl ether* solidified in contact with a little light petroleum (b. p. 40—60°) and then separated from acetone–light petroleum (b. p. 60—80°) in pale yellow needles (1·12 g.), m. p. 118—120°, with a negative ferric reaction and infrared max. at 1701 (aryl ketone), 1672 cm.$^{-1}$ (araldehyde) [Found: C, 68·7; H, 5·7; OMe, 19·5. $C_{14}H_{12}O_3(OMe)_2$ requires C, 68·7; H, 5·7; OMe, 19·7%]. The *monosemicarbazone* crystallised from 95% alcohol in needles, m. p.

[1] Part I, Evans, McGookin, Jurd, Robertson, and Williamson, *J.*, 1957, 3510.
[2] Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 1605.

208—211° (Found: C, 61·5; H, 5·7; N, 11·4. $C_{19}H_{21}O_5N_3$ requires C, 61·4; H, 5·6; N, 11·3%), and the *mono*-2 : 4-*dinitrophenylhydrazone* from ethyl acetate in scarlet needles, m. p. 200° (Found: C, 58·2; H, 4·5; N, 11·3. $C_{24}H_{22}O_8N_4$ requires C, 58·3; H, 4·4; N, 11·3%).

3-*Acetyl*-2-*benzyloxy*-4 : 6-*dimethoxy*-ω-*nitrostyrene* (II).—The foregoing benzyl ether (1 g.) was heated with nitromethane (0·2 ml.) in pyridine (4 ml.) containing piperidine (4 drops) at 100° for 1 hr., the cooled mixture was poured into 2N-hydrochloric acid (40 ml.), and the solution extracted with benzene–ether. Evaporation of the dried extracts left a gum which on crystallisation from dilute alcohol gave 3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxy*-ω-*nitrostyrene* in yellow needles (0·45 g.), m. p. 121—122°, infrared max. at 1701 (aryl ketone), 1616 (aryl conjugated double bond), 1567 (aromatic and nitro), and 1299 cm.$^{-1}$ (nitro) (Found: C, 63·7; H, 5·3; N, 4·0. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·4; N, 3·9%).

When a mixture of the same benzyl ether (0·15 g.), excess of nitromethane (0·2 ml.), methanol (1 ml.), and piperidine (2 drops) was kept overnight and then diluted with water α-(3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxyphenyl*)-β-*nitro*-α-(*nitromethyl*)*ethane* (0·1 g.) was obtained in needles, m. p. 143—145° after purification from dilute alcohol, infrared max. at 1704 (aryl ketone), 1560, 1548 (nitro), and 1351 cm.$^{-1}$ (nitro) (Found: C, 57·3; H, 5·3; N, 6·6. $C_{20}H_{22}O_8N_2$ requires C, 57·4; H, 5·3; H, 6·7%).

3-*Acetyl*-2-*hydroxy*-4 : 6-*dimethoxyphenylacetaldehyde Dimethyl Acetal* (VI).—A mixture of 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene (70 mg.), iron filings (0·2 g.), alcohol (2·4 ml.), and acetic acid (0·4 ml.) was gently warmed for 11 min., filtered (residue washed with alcohol), and poured into water (40 ml.). The liquor was neutralised with sodium hydrogen carbonate and extracted with ether (20 ml. × 5), and the residual oil left on evaporation of the dried extract was boiled with methanol (20 ml.) containing concentrated sulphuric acid (0·1 ml.) for 1 hr., cooled, treated with barium carbonate (2 g.), filtered, and evaporated. The residue was triturated with water and extracted with ether, giving a dark gum which was chromatographed from benzene on silica powder. Crystallised from methanol, the product left on evaporation of the benzene eluate gave the dimethyl acetal of 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde in pale yellow needles (*ca.* 10 mg.), m. p. and mixed m. p. 114—116°, having an infrared absorption spectrum identical with that of the natural specimen.

3-*Acetyl*-2-*benzyloxy*-4 : 6-*dimethoxycinnamic Acid*.—Interaction of 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (0·86 g.) with malonic acid (1·16 g.) in pyridine (2 ml.) and piperidine (0·2 ml.) at 100° for 3 hr. followed by dilution of the cooled mixture with water (10 ml.) and alcohol (2 ml.) gave 3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxycinnamic acid* as a yellow solid (0·3 g.), m. p. 180—186°, which on purification from 50% acetic acid formed yellow needles (0·25 g.), m. p. 185—187° [Found: OMe, 17·8%; equiv., 352. $C_{18}H_{14}O_4(OMe)_2$ requires OMe, 17·4%; equiv., 356]. Crystallised from benzene containing a little acetone the acid formed yellow rhombs (0·25 g.), m. p. 185·5—187°, with infrared max. at 1704 (aryl ketone), and 1675 cm.$^{-1}$ (acid carbonyl), which retained solvent of crystallisation [Found: C, 69·7; H, 5·6; OMe, 16·0. $C_{18}H_{14}O_4(OMe)_2,0{\cdot}5C_6H_6$ requires C, 69·8; H, 5·8; OMe, 15·4%]. On being boiled with methanol (30 ml.) containing concentrated sulphuric acid (1 ml.) for 6½ hr. the compound (50 mg.) underwent esterification and simultaneous debenzylation, giving *methyl* 3-*acetyl*-2-*hydroxy*-4 : 6-*dimethoxycinnamate* which separated from ethyl acetate in pale yellow needles (20 mg.), m. p. 210°, with a dark green ferric reaction in alcohol [Found: C, 59·9; H, 6·0; OMe, 33·5. $C_{11}H_7O_3(OMe)_3$ requires C, 60·0; H, 5·7; OMe, 33·2%].

2-*Benzyloxy*-ω : 4 : 6-*trimethoxyacetophenone* was prepared by heating 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone [3] (45·2 g.) with benzyl bromide (24 ml.) and potassium carbonate (28 g.) in boiling acetone (500 ml.) for 7·5 hr. Crystallised from 95% alcohol, the compound formed needles (39·2 g.), m. p. 74—76°, having a negative ferric reaction and a purple 3 : 5-dinitrobenzoic acid–aqueous sodium hydroxide reaction [Found: C, 68·5; H, 6·4; OMe, 29·8. $C_{15}H_{11}O_2(OMe)_3$ requires C, 68·3; H, 6·3; OMe, 29·4%].

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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[3] Row and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 23.

1004. *Studies in the Pyrolysis of Organic Bromides. Part VII.* The Maximally Inhibited Decomposition of* cyclo*Pentyl Bromide.*

By M. N. Kale and Allan Maccoll.

Gas-phase pyrolysis of *cyclo*pentyl bromide over the temperature range 300—360° proceeds homogeneously according to a first-order law by a mixed chain and unimolecular mechanism, the latter predominating. The temperature-dependence of the rate constants was represented by $k = 1{\cdot}29 \times 10^{13}$ exp $(-41{,}590/RT)$ (sec.$^{-1}$). The reaction is also homogeneous and of the first order in the presence of added *cyclo*hexene, so under these conditions the mechanism is unimolecular. The rate constants were fitted to the equation, $k = 6{\cdot}92 \times 10^{13}$ exp $(-43{,}700/RT)$ (sec.$^{-1}$). The relation of this result to those for other secondary bromides and to certain reactions in polar solvents is discussed in the light of an analogy proposed by Maccoll and Thomas.

In continuation of our investigations into the structural factors influencing the rates of pyrolysis of organic bromides, the present work describes a study of the pyrolysis of *cyclo*pentyl bromide in the absence and in the presence of *cyclo*hexene. In Part V,[1] the pyrolysis of *cyclo*hexyl bromide was shown to proceed by a homogeneous unimolecular mechanism, involving elimination of hydrogen bromide. In particular, the rate of pyrolysis was unaffected by added *cyclo*hexene. In the present case, however, a small, but significant, difference was caused by added *cyclo*hexene.

After this work was complete, Price, Shaw, and Trotman-Dickenson [2] reported results confirming ours on the thermal decomposition of *cyclo*pentyl bromide, except as regards the effect of *cyclo*hexene. This difference may be due to the low molar ratio of *cyclo*hexene used by Price *et al.* A further significant difference was the presence of short induction periods, corresponding to 2—3% of decomposition, not observed by us for this or any bromide decomposing by a unimolecular mechanism.

Experimental

*cyclo*Pentyl bromide was prepared from *cyclo*pentanol and hydrogen bromide. On distillation through a 1-m. column packed with glass helices, a fraction having b. p. 136·0°/765 mm., n_D^{25} 1·4867, was collected (lit., 135—136°/760 mm.,[3] n_D^{25} 1·4866 [4]). Decomposition of the bromide was followed (cf. earlier papers) by measuring the rate of pressure increase in an all-glass apparatus. The stoicheiometry of the reaction was verified by comparing the amount decomposition calculated from the pressure increase with that obtained by direct titration of the hydrogen bromide produced. The irreproducibility found by Price *et al.* was not apparent in the present work.

Justification for the overall reaction

$$C_5H_9Br = C_5H_8 + HBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in the absence and presence of *cyclo*hexene is shown in Table 1, which presents a representative selection of results obtained. Runs marked h were carried out in the presence of *cyclo*hexene.

Table 1. *Decomposition at* 318·2°.

Decompn. (%) (press.)	12·4	22·5h	29·0	47·7h	66·1	72·3h	85·7
Decompn. (%) (anal.)	12·2	22·0h	28·6	49·0h	64·9	73·5h	84·5

Rate constants have been calculated on the basis of eqn. (1). The homogeneity of the reaction was tested by increasing the surface : volume ratio of the reaction vessel by a factor of five, by

* Part VI, *J.*, 1955, 2454.

[1] Green and Maccoll, *J.*, 1955, 2449.
[2] Price, Shaw, and Trotman-Dickenson, *J.*, 1956, 3856.
[3] Moller and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1080.
[4] Rogers and Roberts, *ibid.*, 1946, **68**, 843.

TABLE 2. *Effect of surface : volume ratio* (10^4k_1 in sec.$^{-1}$).

	No *cyclo*hexene		*cyclo*Hexene added	
Temp.	Packed (obs.)	Unpacked (calc.)	Packed (obs.)	Unpacked (calc.)
341·8°	20·3	20·5	19·2	19·5
324·8	7·89	7·85	7·06	7·08
306·8	2·72	2·64	2·32	2·27

TABLE 3. *Effect of variation of initial pressure.*

Uninhibited reaction at 327·8°.

p_0 (mm.)	12·2	20·2	28·7	30·1	45·0	66·0	91·0
10^4k_1 (sec.$^{-1}$)	9·11	9·21	8·83	9·60	9·29	8·32	8·57

Inhibited reaction at 340·5°.

p_0 (mm.)	44·0	45·0	50·0	57·0	68·0	70·5	88·0
10^4k_1 (sec.$^{-1}$)	19·0	17·9	17·7	19·2	17·7	18·5	18·8

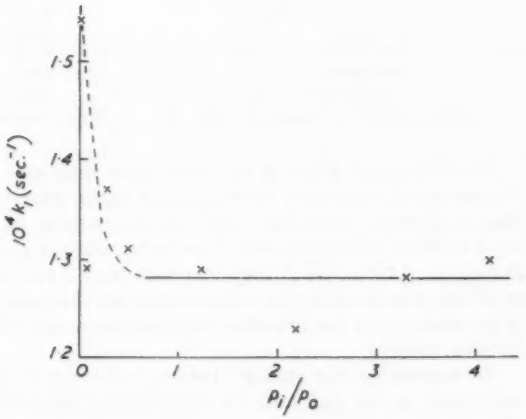
TABLE 4. *Temperature-dependence.*

	Uninhibited					Inhibited				
Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)	Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)	Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)	Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)
361·6°	6	59·7	327·8°	7	9·19	361·6°	6	59·2	327·8°	3	8·34
353·1	6	38·6	324·8	3	7·72	350·8	3	31·7	324·8	5	7·14
345·8	5	25·5	318·8	4	5·64	345·5	4	25·2	318·1	3	4·32
340·5	5	19·5	311·4	6	3·40	340·5	8	18·3	306·3	4	2·07
340·3	2	18·6	298·1	1	1·54	340·3	5	17·8	303·5	5	1·80
335·8	5	14·3				338·8	5	16·1	301·8	3	1·63
						333·3	12	10·9	298·1	7	1·29

means of thin-walled glass tubing. The results are in Table 2. Each observed velocity constant is the mean of five determinations. The calculated values are obtained from the appropriate Arrhenius equations. In view of the large increase in the surface : volume ratio, the reaction is clearly homogeneous.

Effect of cyclohexene on the rate of pyrolysis at 298·1°.

(*p* = *pressure of inhibitor*, p_0 = *pressure of bromide.*



To verify the first-order nature of the decomposition, a number of runs were done with varying initial pressures of *cyclo*pentyl bromide. The first-order constants derived (Table 3) show the first-order nature of the decomposition since in neither case is there a regular trend with initial pressure. For the inhibited runs, p_i/p_0 was at least unity. The effect of added *cyclo*hexene is shown in the Figure, which gives the results of experiments at 298·1°, where the effect is greatest: there is a small but significant decrease from the value in the absence of *cyclo*hexene ($1·53 \times 10^{-4}$ sec.$^{-1}$, calculated from the Arrhenius equation, to $1·29 \times 10^{-4}$ sec.$^{-1}$). At the highest temperature of the range studied (361·6°), the difference is much smaller

($59{\cdot}7 \times 10^{-4}$ and $59{\cdot}2 \times 10^{-4}$ sec.$^{-1}$), indicating that the reaction in the presence of *cyclo*hexene had a somewhat greater activation energy than that of *cyclo*pentyl bromide alone.

The variations of the first-order rate constants with temperature shown in Table 4 lead to the Arrhenius equations:

Uninhibited; $\log k = 12{\cdot}11 - 41{,}590/2{\cdot}303RT$

Inhibited; $\log k = 12{\cdot}84 - 43{,}700/2{\cdot}303RT$

The fit is good in both cases.

Discussion

The results described above show that the gas-phase pyrolysis of *cyclo*pentyl bromide in seasoned vessels is a first-order reaction, homogeneous in the absence or presence of *cyclo*hexene. However, in the latter case, at the lowest temperatures used, the rate is lowered some 15% by this addition. The reaction in the presence of *cyclo*hexene can be identified as unimolecular elimination of hydrogen bromide by analogy with decompositions of other bromides studied in the present series. In Part X [5] it will be shown that *cyclo*hexene is a very efficient chain-inhibitor, so the reaction in the absence of *cyclo*hexene may be identified as a mixed unimolecular and chain mechanism, the former predominating. As the reaction proceeds by a mixed mechanism, the Arrhenius parameters are of little fundamental interest. It is worthy of note, however, that the parameters reported by Price *et al.*, namely, $\log A = 11{\cdot}90$ and $E = 41{\cdot}4$ kcal./mole, are in excellent agreement with ours.

The Arrhenius parameters of the secondary bromides so far studied are shown in Table 5. The parameters for *cyclo*pentyl bromide are significantly smaller than the others, though not as small as suggested by Price *et al.* The interpretation of this decrease must await a further discussion of the transition state in gas-phase eliminations.

Table 5.

Bromide	$\log A$	E	Reference
iso-Propyl	13·63	47·8	*a*
sec.-Butyl	13·53	46·5	*b*
*cyclo*Hexyl	13·51	46·1	1
*cyclo*Pentyl	12·84	43·7	This work

a, Maccoll and Thomas, *J.*, 1955, 979. *b*, Kale, Maccoll, and Thomas, unpublished work.

In their paper Price *et al.* show, from their rate constants, at 380°, that the rate of elimination of hydrogen bromide from *cyclo*pentyl bromide is slightly greater than that from *cyclo*hexyl bromide. From a comparison of this rate ratio with that observed for 1-methyl*cyclo*pentyl and 1-methyl*cyclo*hexyl chloride in solution in 80% aqueous alcohol (1 : 125) at 25°,[6] they conclude that "the parallel between the rates of the S_N1 reactions and the molecular eliminations breaks down in this case." Further examination of the evidence in the literature demonstrates, as will be shown, that this conclusion is of dubious validity.

In suggesting the analogy between the rates of unimolecular dehydrohalogenation and those of the S_N1 and $E1$ reactions in polar solvents, Maccoll and Thomas [7] drew attention to the observed rates of elimination from α- and β-methylated ethyl bromides. Trends observed in these series were qualitatively in accord with those met with in S_N1 and $E1$ mechanisms, suggesting that common electronic effects were involved in the two apparently diverse reactions. The argument cannot, of course, be extended to predict quantitative parallelism in rates of reactions which take place at temperatures some 300°

[5] Maccoll and Thomas, *J.*, 1957, 5033.
[6] Brown and Borkowski, *J. Amer. Chem. Soc.*, 1952, **74**, 1894.
[7] Maccoll and Thomas, *Nature*, 1955, **176**, 392.

apart: no more than a broad qualitative agreement is to be expected. The scope and limitations of the analogy will be discussed in greater detail later.

Studies of unsubstituted *cyclo*alkyl compounds have so far been restricted to the benzenesulphonates and toluene-*p*-sulphonates. There is evidence that these compounds react in polar solvents similarly to the halides. The activation energies (kcal./mole) for *cyclo*pentyl and *cyclo*hexyl compounds are:

	Benzenesulphonate [8]	Toluene-*p*-sulphonate [8, 9, 10]
*cyclo*Pentyl	22·7	24·1, 23·7, 27·6
*cyclo*Hexyl	26·8	27·3, 27·0, 27·4

In addition, the relative rates [8,10] in the two cases (at 50°) are 1 : 20 and 1 : 16. Although for 1-methyl*cyclo*alkyl chlorides the rate ratio is 1 : 125, the activation energies are comparable with those quoted above, namely, 20·8 (1-methyl*cyclo*pentyl) and 24·9 kcal./mole (1-methyl*cyclo*hexyl). In a review, de la Mare [11] concludes with regard to the *cyclo*alkyl toluene-*p*-sulphonates that "the reactivity of *cyclo*pentyl derivatives under ionising conditions is an example of steric acceleration." The much greater rate ratio for 1-methyl-*cyclo*alkyl chlorides may thus not unreasonably be ascribed to additional steric acceleration, due to methyl substitution at the seat of reaction. For this reason, the comparison drawn by Price *et al.* is considered unwarranted.

That the results described in this paper conform to, rather than contradict, the proposed analogy can be seen by the following argument. In the first place, the difference in activation energy (2·4 kcal./mole) has the same sign as that for the S_N1 reactions in solution, namely, *cyclo*hexyl > *cyclo*pentyl. This in itself is reasonable evidence, as it is known for the dehydrobromination reaction that the frequency factors are sensibly constant over the series of compounds studied, the major factor influencing the rate being the activation energy. Secondly, the rate ratios for the secondary bromides so far studied (k_{RX}/k_{PrX}), namely:

*iso*Propyl	*sec.*-Butyl	*cyclo*Hexyl	*cyclo*Pentyl
1	2·4	3·2	5·1

at 330° show that, of the *cyclo*alkyl bromides, the *cyclo*hexyl compound more closely resembles the *sec.*-butyl compound in rate. This is also the conclusion drawn by de la Mare [11] from solvolyses of the halides and of the toluene-*p*-sulphonates. Use of 330° in calculating the rate ratios is justified on the grounds that this is the mean temperature of the range experimentally studied, and as such is least likely to suffer from experimental errors in the Arrhenius parameters. Finally, though not much significance can be placed on this because of the long extrapolation, it is of interest that the rate ratio for the gas-phase reactions calculated at 25° is about 1 : 12, a value not dissimilar from those reported for the benzene and toluene-*p*-sulphonates.

The final conclusion to be drawn is that elimination from *cyclo*pentyl and *cyclo*hexyl bromide, far from being an exception to the proposed analogy between gas-phase eliminations and the S_N1 and $E1$ reactions in solution as suggested by Price, Shaw, and Trotman-Dickenson, actually provides further confirmation of a rather striking kind.

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[8] Brown and Ham, *J. Amer. Chem. Soc.*, 1956, **78**, 2735.
[9] Winstein, Morse, Grunewald, Jones, Corse, Triffan, and Marshall, *ibid.*, 1952, **74**, 1127.
[10] Roberts and Chambers, *ibid.*, 1951, **73**, 5034.
[11] de la Mare, "Progress in Stereochemistry," ed. W. Klyne, Butterworths, London, 1954, Vol. I p. 105.

1005. *Studies in the Pyrolysis of Organic Bromides. Part VIII.* Pyrolysis of* tert.*-Amyl Bromide.*

By G. D. Harden.

tert.-Amyl bromide decomposes in the range 220—270° according to a first-order rate law, to give hydrogen bromide and an olefin, which infrared studies indicate is 2-methylbut-2-ene. *cyclo*Hexene has no effect on the rate, and relatively large pressures of bromine cause only a slight acceleration. In seasoned reaction vessels the reaction is homogeneous. The rate is given by $k_1 = 3{\cdot}98 \times 10^{13} \exp(-40{,}500/RT)$ sec.$^{-1}$) and it is concluded that the decomposition occurs by unimolecular elimination of hydrogen bromide.

In studies designed to correlate the gas-phase mechanism of decomposition of organic bromides with molecular structure, Maccoll *et al.* (Parts I—VI [1]) have so far established three different homogeneous mechanisms for the pyrolysis of alkyl bromides. (1) Allyl bromide decomposes by a radical, non-chain process (Part I), as a result of rupture of the C–Br bond; (2) *n*-propyl bromide decomposes by a bromine-atom chain mechanism (Part II); (3) *iso*propyl (Part III), *sec.*-butyl (Part IV), *cyclo*hexyl (Part V), and *tert.*-butyl bromide (Part VI) decompose in seasoned vessels by unimolecular elimination of hydrogen bromide. The present investigation was undertaken to determine the effect of replacing a primary C–H bond (cf. *tert.*-butyl bromide) by a secondary one, on the rate of elimination of hydrogen bromide. No physicochemical studies of the kinetics of the pyrolysis of *tert.*-amyl bromide have been reported hitherto.

Experimental

The apparatus employed was essentially that described in Part I.[1] *tert.*-Amyl bromide was introduced from a vapour reservoir. Reaction vessels were seasoned by the pyrolysis products of allyl bromide.

tert.-Amyl bromide, prepared from pure *tert.*-amyl alcohol by Bryce-Smith and Howlett's method,[2] was fractionally distilled, and collected at 48·8°/100 mm. The refractive index was n_D^{25} 1·4392 (cf. 1·4421 reported by Brown and Stern [3]).

The rate of decomposition was measured by following the rate of pressure change on the basis of the equation $C_5H_{11}Br \longrightarrow C_5H_{10} + HBr$. Because of the rapid recombination of the products of reaction during condensation, it was not possible to compare rate constants calculated from the pressure increase with those derived from the hydrogen bromide produced (cf. *tert.*-butyl bromide, Part VI). However, circumstantial evidence confirms the stoicheiometry of the reaction. Thus a series of runs was followed until no further increase in pressure was detectable. In all cases the final pressure (p_t) reached a value nearly double the initial pressure (p_0) as shown in Table 1.

Table 1. *Ratio of final to initial pressure.*

Temp.	269·4°	269·4°	269·4° *	263·3°	254·1°	247·7°	242·3°	242·3°	242·3°	235·6°	233·1°
p_0 (mm.) ...	257	203	189	199	252	209	272	269	136	272	266
p_t/p_0	1·85	1·90	1·83	1·81	1·85	1·86	1·83	1·80	1·90	1·76	1·69

* In the presence of 57 mm. of *cyclo*hexene.

According to the proposed scheme, p_t/p_0 should reach a value of 2. The fact that this ratio is always less than 2 is attributed to two factors. (*a*) An equilibrium may occur between *tert.*-amyl bromide and its decomposition products; this would be in keeping with the behaviour of

* Part VII, preceding paper.

[1] Maccoll *et al.*, *J.*, 1955, 965 (Part I), 973 (Part II), 979 (Part III), 2445 (Part IV), 2449 (Part V), 2454 (Part VI).

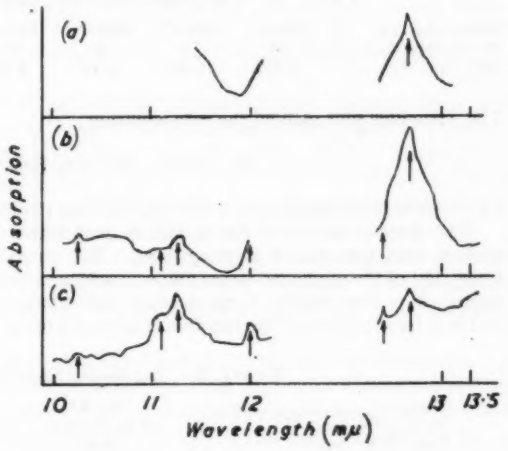
[2] Bryce-Smith and Howlett, *J.*, 1951, 1141.

[3] Brown and Stern, *J. Amer. Chem. Soc.*, 1950, **72**, 5068.

the bromides already investigated, in particular with that of *tert.*-butyl bromide (Part VI; [1] Kistiakowsky and Stauffer [4]). (*b*) In the apparatus used, the dead-space effect will be of some importance; the difficulty of estimating this effect quantitatively prevented precise investigation of the equilibrium. Further evidence of the stoicheiometry is that no uncondensable gases were formed even in long runs at high temperatures.

The olefin C_5H_{10} may be 2-methylbut-2- or -1-ene. Recombination was so rapid that the olefin could not be separated from the hydrogen bromide, but the olefin was identified as 2-methylbut-2-ene by infrared analysis of the hot reaction mixture in the range 10—13·5 μ.* In the Figure the spectrum of the reaction mixture in the given wavelength range is compared with that of 2-methylbut-2-ene. It is possible that a small amount of 2-methylbut-1-ene is also formed.

Addition of hydrogen bromide to either 2-methylbut-2- or -1-ene under the conditions used here would give *tert.*-amyl bromide, according to Markownikow's rule. It is of interest that if



Infrared spectrum of the products of pyrolysis of tert.*-amyl bromide.*
(*a*, *c*) *Reaction products.*
(*b*) *Pure 2-methylbut-2-ene.*

the reaction is stopped by condensing the products, and then re-started, both the original initial pressure and the original rate of decomposition are approximately reproduced. Table 2 shows the results of two such runs.

TABLE 2. *The effect of re-starting a run.*

Temp.	p_0 (mm.)	10^4k_1 (sec.$^{-1}$)	p_1 (mm.)	p_0'	$10^4k_1'$ (sec.$^{-1}$)
247·7°	252	5·67	385·5	257	5·37
247·7	241	6·13	380·5	254	6·08

It was also found that when a mixture of approximately equal pressures of 2-methylbut-2-ene and hydrogen bromide was admitted to the reaction vessel and then condensed out and readmitted, a marked decrease in pressure occurred, followed by a gradual increase. The rate of decomposition of the bromide was then calculated by assuming the decrease to be due to addition and the increase to decomposition of the bromide formed. The first-order rate plot led to an initial rate of $7·18 \times 10^{-4}$ sec.$^{-1}$, close to the rate calculated from the Arrhenius plot ($7·41 \times 10^{-4}$ sec.$^{-1}$).

A series of runs with varying initial pressures was carried out in order to verify the order of the reaction. The results are in Table 3. Graphs were drawn for reactions of order 0·5, 1, and 1·5, and in all cases the first and third of these were markedly curved, whereas the first-order plots were linear up to about 40% reaction. Further, as can be seen in Table 3, the first-order

* The author is indebted to Mr. D. W. Watson for assistance with the infrared analysis.

[4] Kistiakowsky and Stauffer, *J. Amer. Chem. Soc.*, 1937, **59**, 165.

constants did not vary significantly over a five-fold range of initial pressure. It may be concluded that the reaction is of the first order. The fact that the first-order constants begin

TABLE 3. *The pressure dependence of the velocity constants.*

p_0 (mm.)	364	352	296	290	252	241	224·5	217·5	209	121	79·2
10^4k_1 (sec.$^{-1}$) ...	6·12	5·92	5·87	6·22	5·67	6·13	6·19	5·68	6·13	5·80	6·17

to fall in the later stages of the reaction is a direct consequence of the failure of the ratio p_t/p_0 to reach 2.

The temperature range 220—270° was next systematically explored. As Table 3 indicates the characteristic range of variation of rate constants obtained, it is unnecessary to report all the results in detail: Table 4 summarises the experimental results.

TABLE 4. *The temperature dependence of the velocity constant.*

Temp.	223·4°	233·1°	235·6°	242·3°	247·7°	254·1°	263·3°	269·4°
No. of runs	11	11	9	12	11	11	11	10
10^4k_1 (sec.$^{-1}$)	0·922	1·99	2·43	4·26	5·99	9·95	19·38	28·84

The Arrhenius plot yielded the rate equation

$$k_1 = 3{\cdot}98 \times 10^{13} \exp(40{,}500/\boldsymbol{R}T) \text{ (sec.}^{-1}\text{)}$$

The experimental points all lie close to the best straight line.

The effect of surface on the rate of decomposition was studied by means of runs in a vessel packed with thin-walled Pyrex tubing. The packed vessel had a surface : volume ratio 6·8 times that of the unpacked vessel and was seasoned by the products of pyrolysis of allyl bromide before use. The results (Table 5) show how small is the effect of an increase in surface area and it is concluded that the reaction is homogeneous.

TABLE 5. *Decompositions in a packed vessel.*

Temp.	237·6°	248·7°	260·7°
Mean 10^4k_1 (sec.$^{-1}$)	3·35 (3 runs)	6·86 (3 runs)	15·87 (6 runs)
Calc. 10^4k_1 (sec.$^{-1}$)	2·84	6·61	15·78

In order to identify the mechanism of the pyrolysis, a number of runs were carried out in the presence of added *cyclo*hexene. This substance has been shown [5] to inhibit the chain mode of decomposition of *n*-propyl bromide. The results are in Table 6, p_i being the pressure of added *cyclo*hexene. It is seen that the rate is independent of the *cyclo*hexene pressure. This provides strong evidence against a chain mechanism for the pyrolysis. Further, in the normal runs and also in those with added *cyclo*hexene no induction periods were apparent.

TABLE 6. *Effect of added* cyclo*hexene.*

	At 223·4° k_1 (calc.) = 0·916 × 10^{-4} (sec.$^{-1}$)					At 269·4° k_1 (calc.) = 28·8 × 10^{-4} (sec.$^{-1}$)			
p_i (mm.)	0	48	49	71	88	90	0	55	57	120
p_0 (mm.)	—	207	195·5	210	203·5	213	—	108	189	191
10^4k_1 (sec.$^{-1}$)	0·922 *	0·940	0·886	0·899	0·908	0·864	28·8 *	30·0	29·8	28·7

* Mean of 10 runs.

It has been shown (Part I) that allyl bromide decomposes by a mechanism involving a primary splitting off of a bromine atom. Further, Thomas (unpublished work) has shown that decomposing allyl bromide is capable of catalysing the decomposition of those normal bromides for which the uninhibited mode of decomposition involves, at least in part, bromine atom chains. In addition, Thomas has shown that decomposing allyl bromide is capable of stimulating a chain mechanism in some compounds that normally decompose by a unimolecular mechanism.

[5] Maccoll and Thomas, *J.*, 1957, 5033.

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Similarly, molecular bromine, which thermally dissociates into bromine atoms, has been shown by Daniels and Veltman [6] to catalyse the decomposition of ethyl bromide. For these reasons, the decomposition of *tert.*-amyl bromide was investigated in the presence of both allyl bromide and bromine. The results are in Table 7, where p_s is the pressure of added stimulant. Allyl

TABLE 7. *Effects of allyl bromide and bromine as stimulants (at 254·1°).*

	Allyl bromide					Bromine		
p_s (mm.)	0	52	69	102	149	37	59	69
p_0 (mm.) [a]	—	236	210	230	227	232	164·5	101·5
10^4k_1 (sec.$^{-1}$) [b] ...	9·95	9·72	10·2	10·0	9·89	9·89	10·2	11·6

[a] Mean of 11 runs. [b] 10^4k_1 (calc.) = 9·75 sec.$^{-1}$.

bromide appears to have little effect on the rate, whereas bromine at high pressures appears to catalyse it slightly. A quantitative study of the sensitised decomposition was not undertaken in the case of bromine since the sensitised reaction did not show good first-order behaviour, probably owing to side reactions between bromine and *tert.*-amyl bromide or the olefin.

The absence of induction periods, and the lack of inhibition by *cyclo*hexene, show that the mechanism of decomposition is unlikely to be a radical–atom chain process. The view is substantiated by the experiments with added allyl bromide and bromine. Further, the magnitude of the activation energy (40·5 kcal./mole) rules out the possibility of a radical non-chain process, since for such a mechanism, the activation energy must be of the order of the C–Br bond dissociation energy (~64 kcal./mole). The fact that the reaction is homogeneous and of the first order, together with the evidence cited above, proves that the decomposition occurs by unimolecular elimination of hydrogen bromide. The similarity of the activation energy to that for *tert.*-butyl bromide (42·2 kcal./mole) (Part VI) confirms this.

That the major olefinic product is 2-methylbut-2-ene implies that the elimination of hydrogen is easier from CH than from CH_2, in line with the fact that decomposition of *tert.*-amyl bromide is 3·2 times faster than that of *tert.*-butyl bromide at 250°. This suggests that the maximum amount of 2-methylbut-1-ene in the products should be of the order of 20%. That the nature of the C–Br bond is the major factor determining the rate of elimination of hydrogen bromide has been stated before.[7] The present work shows that the nature of the C–H bond plays a rôle, albeit a minor one.

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[6] Daniels and Veltman, *J. Chem. Phys.*, 1937, **7**, 756.
[7] Green, Harden, Maccoll, and Thomas, *ibid.*, 1953, **21**, 170.

1006. *Studies in the Pyrolysis of Organic Bromides. Part IX.*[1] *The Pyrolysis of 2-Bromo-2 : 3-dimethylbutane.*

By G. D. Harden and Allan Maccoll.

Over the temperature range 210—260°, the pyrolysis of 2-bromo-2 : 3-dimethylbutane in seasoned vessels is a homogeneous, first-order reaction, the rate constant being $k_1 = 3{\cdot}47 \times 10^{13} \exp(-39{,}000/RT)$ (sec.$^{-1}$). At the lower temperatures there may be a small contribution from a chain mechanism, but the predominant mechanism is the unimolecular elimination of hydrogen bromide. Some general conclusions are drawn as to the mode of decomposition of *tert.*-alkyl bromides.

Parts VI and VIII [1] described the pyrolyses of *tert.*-butyl and *tert.*-amyl bromide. While the C–Br bond in both these compounds is tertiary, the C–H bond involved in the elimination of hydrogen bromide is primary in the former and secondary in the latter case. The ratio of the rates at 250° was 3·2. It is of interest to examine a case where the C–H bond is tertiary, the simplest example of such a compound being 2-bromo-2 : 3-dimethylbutane. There has not previously been a physicochemical study of the pyrolysis of this compound.

Experimental

According to Kishner,[2] the required bromide can be readily obtained from 2 : 3-dimethylbutan-2-ol by treatment with hydrogen bromide. Interaction of methylmagnesium iodide and methyl *iso*propyl ketone, extraction with ether, and distillation of the product gave 2 : 3-dimethylbut-2-ene, b. p. 72°. This was treated with excess of hydrogen bromide solution, and the organic layer collected, washed, and dried; distillation gave a bromide, b. p. 61·8—62·2°/72 mm., n_D^{25} 1·4500 (Krishner [2] reports 1·4501). A second sample, prepared from the alcohol by Bryce-Smith and Howlett's method [3] and fractionated, had b. p. 59·3°/62 mm., n_D^{25} 1·4497. The two samples showed identical kinetic behaviour.

For primary and secondary bromides investigated so far, the stoicheiometry of the decomposition has been shown accurately to be represented as:

$$C_nH_{2n+1}Br = C_nH_{2n} + HBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

However, for the tertiary bromides so far examined, it has not been possible to compare the amount of decomposition derived from pressure measurements with that derived by a direct titration of the acid produced because of the rapid re-addition which occurs during the condensing or vaporisation of the products. However, it is known that *tert.*-butyl and *tert.*-amyl bromides decompose according to equation (1) and that under the conditions of these experiments the olefins produced are *iso*butene and 2-methylbut-2-ene, respectively. With 2-bromo-2 : 3-dimethylbutane, a number of runs at temperatures from 222° to 257° and initial pressures from 100 to 200 mm. gave ratios of final to initial pressure in the range 1·80—1·90, to be compared with the value of 2 demanded by equation (1). Dead-space errors [4] and the reverse reaction suffice to explain the small discrepancy. Further, no gases uncondensable in liquid air (*e.g.*, hydrogen or methane) were detected in the products. Again, when the products were condensed out and then re-admitted to the reaction vessel, the pressure was observed to have fallen to a value intermediate between the initial value and the value at the time of condensation. From experiments of this type, the degree of recombination may be estimated. Thus at 229° and an initial pressure of 317 mm. the reaction was stopped when the pressure had risen to 475 mm.: the initial pressure on re-admission was 359 mm., corresponding to 73% of recombination. Another experiment gave 67% of recombination. It was further observed that the pressure–time curve obtained after re-admission was superimposable on the original curve, after a suitable change of origin. These observations confirm the suggested stoicheiometry.

[1] Part VI, *J.*, 1955, 2454; Part VII and VIII, preceding papers.
[2] Kishner, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 165; *Chem. Zentr.*, 1912, **16**, *I*, 2025.
[3] Bryce-Smith and Howlett, *J.*, 1951, 1141.
[4] Allen, *J. Amer. Chem. Soc.*, 1934, **56**, 2053.

Since no hydrogen or methane was formed in the pyrolysis, three possibilities remain:

$$CHMe_2{\cdot}CMe_2Br \longrightarrow \begin{cases} CMe_2{:}CMe_2 + HBr & (A) \\ CHMe{\cdot}CMe{:}CH_2 + HBr & (B) \\ CHMe{:}CMe_2 + MeBr & (C) \end{cases}$$

Reaction (*C*) is excluded because (i) elimination of methyl bromide has never been observed from alkyl bromides, and (ii) when approximately equal amounts of 2-methylbut-2-ene and methyl bromide were admitted to the reaction vessel, condensed out, and then re-admitted, no change in pressure occurred, in marked contrast with the behaviour of the reaction products. Hydrogen bromide is involved because when approximately equal pressures of hydrogen bromide and tetramethylethylene were vapourised into the reaction vessel, condensed out, and re-admitted, analysis of the changes of pressure yielded a rate constant $k_1 = 5{\cdot}50 \times 10^{-4}$ sec.$^{-1}$, to be compared with the value of $5{\cdot}86 \times 10^{-4}$ sec.$^{-1}$ calculated from the Arrhenius equation described below. A decision between reaction (*A*) and (*B*) can best be made on the basis of the kinetic behaviour. Production of 2 : 3-dimethylbut-1-ene would require fission of a tertiary C–Br and a primary C–H bond, so the rate should not markedly differ from that for *tert.*-butyl bromide; the observed rate is however, about eight times that of *tert.*-butyl bromide, indicating that scheme (*A*) represents the reaction.

The kinetic studies were carried out in a vessel seasoned by the products of the pyrolysis of allyl bromide. Pressure–time curves were obtained by the technique described previously, and velocity constants were derived from the expression, $p_t = 2p_0 - P_t$, where p_0 is the initial pressure of the bromide, p_t its pressure at time t, and P_t is the total pressure at time t. In all cases linearity was obtained in first-order plots up to about 50% decomposition. The invariance of the first-order rate constant with initial pressure is illustrated in Table 1: over an eight-fold variation of initial pressure the first-order rate constants do not vary significantly.

TABLE 1. *Pyrolyses at* 243·1°.

p_0 (mm.)	372	367	334	294	241	226·5	219	182	161	127·5	94·3	49·2
10^4k_1 (sec.$^{-1}$)	10·19	10·11	10·62	10·39	10·26	10·11	10·26	10·42	10·21	10·21	10·31	10·67

It was next established that the reaction was homogeneous. A packed and seasoned reaction vessel was used, the surface : volume ratio being about four times that of the unpacked vessel. Table 2 shows the results of such experiments; the calculated figure is obtained from the Arrhenius equation.

TABLE 2. *Runs in a packed vessel.*

Temp.	No. of runs	10^4k_1 (sec.$^{-1}$) (obs.)	10^4k_1 (sec.$^{-1}$) (calc.)	Temp.	No. of runs	10^4k_1 (sec.$^{-1}$) (obs.)	10^4k_1 (sec.$^{-1}$) (calc.)
252·5°	5	22·32	20·89	223·5°	4	2·64	2·34
243·4	3	10·84	10·62				

The variation of the velocity constant with temperature is illustrated in Table 3. The results fit the Arrhenius equation:

$$k_1 = 3{\cdot}47 \times 10^{13} \exp(-39{,}000/RT) \text{ (sec.}^{-1}\text{)}$$

In order to test for the presence of reaction chains, runs were carried out in the presence of added *cyclo*hexene, shown by Maccoll and Thomas (following paper) to be a powerful inhibitor of the chain mode of pyrolysis of organic bromides. The results are in Table 4, where p_0 is the initial pressure of the bromide and p_i the pressure of *cyclo*hexene.

TABLE 3. *Effect of temperature.*

Temp.	256·6°	250·2°	243·1°	235·5°	229·0°	221·8°	213·0°
No. of runs	12	12	12	12	10	12	11
10^4k_1 (sec.$^{-1}$)	26·19	17·56	10·31	5·97	3·54	1·97	0·979

Although there is no effect due to *cyclo*hexene at 257°, there is a small but increasing effect as the temperature is lowered: at about 214° the reduction is of the order of 6%. This is

barely within the experimental error but is believed to be significant, and suggested that a chain reaction may play a small part in the pyrolysis.

TABLE 4. *Effect of added* cyclo*hexene.*

	At 256·6°				At 243·1°			
p_1 (mm.)	0	123	106	101	0	90	90	83
p_0 (mm.)	—	183·5	184	193	—	192	186	177
10^4k_1 (sec.$^{-1}$) ...	26·2 [a]	26·7	25·6	26·2	10·31 [a]	10·06	10·08	9·75

	At 214·4°					At 213·0°					
p_1 (mm.)	0	57	56	51	50·5	0	229	113	93	60·5	32
p_0 (mm.)	—	153	188	104	170·5	—	167	234	193	108	94
10^4k_1 (sec.$^{-1}$) ...	1·13 [b]	1·10	1·03	1·05	1·09	0·98 [a]	0·92	0·88	0·98	0·80	0·92

[a] Mean of 12 runs. [b] Calc. from Arrhenius plot.

As a result, the effect of chain stimulants was investigated, *e.g.*, of allyl bromide and bromine. The latter has been shown to catalyse the pyrolysis of ethyl bromide [5] whereas the former has been shown by Thomas (unpublished work) both to catalyse the decomposition of those substances which normally decompose by a chain mechanism and to induce a chain mode of decomposition in certain others. In both cases, Thomas has shown that in the presence of an inhibitor

TABLE 5. *Effect of stimulants* (*at* 235·5°).

	Allyl bromide						Bromine				
p_s (mm.)	0	33	57	95	23	35	0	40	71	37	39
p_1 (mm.)	0	0	0	0	53	74	0	0	0	81	67
p_0 (mm.)	—	199	177	210	125	159	—	217	223	279	210
10^4k_1 (sec.$^{-1}$) ...	5·97 [a]	6·94	7·18	7·16	5·86	5·81	5·97 [a]	7·09	8·89	6·00	6·09

[a] Mean of 12 runs.

such as *cyclo*hexene the catalysed rate is reduced to the normal value. The behaviour of 2-bromo-2 : 3-dimethylbutane under these conditions is shown in Table 5, p_s being the pressure of stimulant. It is concluded that the reaction can be catalysed by allyl bromide or bromine, and that the catalysis can be inhibited by addition of *cyclo*hexene.

DISCUSSION

The main points that have emerged from the experimental study are: (1) 2-Bromo-2 : 3-dimethylbutane decomposes cleanly into 2 : 3-dimethylbut-2-ene (main product) and hydrogen bromide in the temperature range 213—257°. (2) The reaction is homogeneous and of the first order, over an initial pressure range of 50—400 mm. (3) Added *cyclo*hexene has only a barely significant effect on the rate and that only at the lower temperatures. (4) Added allyl bromide and bromine catalyse the decomposition, such catalysis being inhibited by the addition of *cyclo*hexene.

From these facts, it may be deduced that the predominant mechanism is a unimolecular elimination of hydrogen bromide, through a four-centre transition state. A radical non-chain mechanism,[1] such as that suggested by Daniels and Veltman,[5] is ruled out by the activation energy required, which is the C–Br bond dissociation energy (60 kcal./mole). This is in keeping with the observed behaviour of the other tertiary bromides studied.[1] However there is an additional feature of the pyrolysis of the present compound, namely, its capacity to support a chain mode of decomposition in favourable circumstances. Now with *iso*propyl bromide there is no evidence of a chain mechanism, but with *sec.*-butyl bromide at the lower temperatures there appears to be a small contribution by a chain mechanism. It appears that a very significant factor in the facilitating of a chain

[5] Daniels and Veltman, *J. Chem. Phys.*, 1939, **7**, 756.

mode of pyrolysis is the presence of a weakened C–H bond, which conceivably reduces the activation energy of attack by a bromine atom on the present bromide:

$$Br + C_nH_{2n+1}Br \longrightarrow \cdot C_nH_{2n}Br + HBr \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Evans [6] has given the values 97, 94, and 89 kcal./mole for the bond-dissociation energies of primary, secondary, and tertiary C–H bonds in ethane, propane, and *iso*butane, based on Stevenson's electron-impact work. It is to be expected that this variation in bond-dissociation energy would to some extent be repeated in the activation energies of reactions (2). This view is substantiated by direct determination of the activation energies of reaction (2) for ethane and *iso*butane, by Van Artsdalen and his co-workers,[7] the respective values being 13·3 and 11·4 kcal./mole.

Some General Observations on the Pyrolysis of Tertiary Organic Bromides.—All the tertiary bromides so far studied decompose either entirely or predominantly by unimolecular elimination of hydrogen bromide. The pre-exponential factors, activation energies, and rates relative to *tert.*-butyl bromide at 250° are shown in Table 6. The activation energy decreases in the series as the C–H bond changes from primary to secondary to tertiary. Though the pre-exponential factor decreases in the same order, the activation energy factor is dominant over the temperature range studied, and so the rate constant slowly increases as the C–H bond strength is reduced. This slow variation in rate contrasts strongly with that observed in the series ethyl, *iso*propyl, *tert.*-butyl bromide, where the relative rates [8] at 380° are in the ratio 1 : 170 : 32,000. This bears out the assertion [8] that the environment of the C–Br bond to be broken is the major factor determining the rate of elimination of hydrogen bromide.

TABLE 6.

Compound	$10^{-13}A$ (sec.$^{-1}$)	E (kcal./mole)	Relative rate
C_4H_9Br	10	42·2	1
$C_5H_{11}Br$	3·98	40·5	3·2
$C_6H_{13}Br$	3·47	39·0	7·5

Of interest too is the trend in the A factors for the elimination of hydrogen bromide per β-hydrogen atom. Since there are 9, 2, and 1 β-hydrogen atoms respectively for *tert.*-butyl bromide, *tert.*-amyl bromide, and 2-bromo-2 : 3-dimethylbutane, the new A factors (A') become 1·11, 1·99, and $3·47 \times 10^{13}$ sec.$^{-1}$ respectively. Since A' increases down the series, and E decreases, the rate sequence at all temperatures for elimination per β-hydrogen atom is *tert.*-butyl bromide > *tert.*-amyl bromide > 2-bromo-2 : 3-dimethylbutane, a simplicity of behaviour not apparent in A'. The assumption underlying this analysis is that in the transition state a given β-hydrogen atom is involved, which is, of course, satisfied by the four-centre transition state.

TABLE 7. *Mechanism of decomposition.*

	Unimolecular	Chain	Stimulated
tert.-Butyl bromide	+	—	—
tert.-Amyl bromide	+	—	+
2-Bromo-2 : 3-dimethylbutane	+	+ (?)	+

The behaviour of the three tertiary bromides already studied, as regards the mode of decomposition and the ability to stimulate reaction chains, is summarised in Table 7.

[6] Evans, *Discuss. Faraday Soc.*, 1951, **10**, 1.
[7] Anderson and Van Artsdalen, *J. Chem. Phys.*, 1944, **12**, 479, 1944; Hormats and Van Artsdalen, *ibid.*, 1951, **19**, 778.
[8] Green, Harden, Maccoll, and Thomas, *ibid.*, 1953, **21**, 178.

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It is tempting to attribute the increasing tendency down the series towards a chain mechanism to the progressive changing of a β-hydrogen atom from primary to secondary to tertiary. Similarly, with primary bromides (ethyl, *n*-propyl, *iso*butyl) chains appear to be much more readily established with *iso*butyl than with *n*-propyl bromide (Harden, unpublished work).

Although re-addition of the products from *tert.*-butyl and *tert.*-amyl bromides goes to completion, that for 2-bromo-2 : 3-dimethylbutane is only partial; this may be explained in terms of the melting points. *iso*Butane, 2-methylbut-2-ene, and 2 : 3-dimethylbut-2-ene melt respectively at −140°, −134°, and −74°. Hydrogen bromide melts at −86° and boils at −67°. On condensing the products and re-vapourising them in the first two cases, the olefin will be melted while the hydrogen bromide is still solid, and this should enable reaction to take place before evaporation is complete. However, in the case of 2 : 3-dimethylbut-2-ene, the hydrogen bromide will have melted and will be close to its boiling point before the olefin melts, and in this way complete re-addition will be prevented.

Mention should be made of other studies [9] of the pyrolysis of *tert.*-butyl bromide, summarised in Table 8 (*E* was incorrectly given in Part VI as 42·0 kcal./mole). The agreement between the various authors' results is on the whole good. However, at the higher temperatures, the half-life of the reaction in Sergeev's study was of the order of 40 sec. It is just possible that with such a short half-life the time of heating of the reactant

TABLE 8.

	Temp. range	$\log_{10} A$	E
Kistiakowsky and Stauffer [9]	235—290°	13·3	40,500
Harden and Maccoll [10]	230—280	14·00	42,200
Sergeev [11]	280—330	13·23	41,000

is sufficient to make the measured rate and thus the activation energy somewhat small; but experimental techniques would have to be considerably refined before an absolute decision could be made as to the Arrhenius parameters. Since, in the current series of papers, interest attaches to structural variations in related compounds, the values of the rate constants used for comparison with each other will be those determined in these laboratories, since these have been measured under strictly comparable conditions.

One of us (G. D. H.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant. Both of us acknowledge many helpful discussions with Dr. P. J. Thomas.

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[9] Kistiakowsky and Stauffer, *J. Amer. Chem. Soc.*, 1937, **59**, 165.
[10] Part VI, ref. 1.
[11] Sergeev, *Doklady Akad. Nauk S.S.S.R.*, 1956, **106**, 299.

1007. *Studies in the Pyrolysis of Organic Bromides. Part X.* The Inhibition of the Chain Mode of Decomposition with Special Reference to* n-*Propyl and* n-*Butyl Bromide.*

By Allan Maccoll and P. J. Thomas.

Olefinic inhibitors are shown to reduce the rate of pyrolysis of *n*-propyl and *n*-butyl bromide. The inhibited rate is independent of the nature, and within limits, of the concentration of the inhibitor. Under conditions of maximum inhibition the decompositions are homogeneous and obey first-order kinetics. It is concluded that the mechanism involved in the decomposition is the unimolecular elimination of hydrogen bromide. The observed rate constants were represented by the Arrhenius equations: †

$$Pr^nBr: \quad k_1 = 7{\cdot}94 \times 10^{12} \exp(-50{,}700/\boldsymbol{R}T) \text{ (sec.}^{-1}\text{)}$$

$$Bu^nBr: \quad k_1 = 1{\cdot}51 \times 10^{13} \exp(-50{,}900/\boldsymbol{R}T) \text{ (sec.}^{-1}\text{)}$$

in the temperature ranges 350—390° and 370—420° respectively.

Introduction to Parts X—XIII.—In Parts III—IX of the present series the pyrolyses of a number of secondary and tertiary alkyl bromides have been described. The only mechanism which played an appreciable part in the decompositions was the single-stage elimination of hydrogen bromide. In the present paper and those following, the series is extended by the study of the inhibited rate of decomposition of a number of primary alkyl bromides and of certain polybromo-compounds, in which a duality of mechanism is observed, reaction proceeding simultaneously by the unimolecular mechanism and by a radical-chain process. Such behaviour was observed with *n*-propyl bromide.[1] It has been possible to isolate and study the unimolecular process by suppressing the chain decomposition by the use of olefinic inhibitors. Thus it is found that the relative contributions of the two modes of decomposition vary from compound to compound, as does the ease with which the chain component may be inhibited. However, various features have emerged which are common to all the examples studied, and it is thus convenient first to summarise the information obtained as to the relative efficiencies of various inhibitors and the kinetic behaviour in the region of partial inhibitions.

The effect of inhibitor concentration. Most of the exploratory work was carried out on *n*-propyl bromide and the results will be discussed with reference to this compound. Its behaviour is typical, and any significant deviations will be reported when the particular compound is being discussed. Fig. 1 shows a series of pressure–time curves for a constant initial pressure of *n*-propyl bromide in the presence of different concentrations of propene. Also shown is an uninhibited run and one completely inhibited with *cyclo*hexene. With low pressures of propene, a marked sigmoid character develops, which is present in neither the uninhibited nor the completely imhibited runs. In fact, as the propene concentration is increased, there is a steady approach to the smooth curve for a first-order reaction. The same behaviour is shown with *cyclo*hexene, and although the concentrations required to reduce the uninhibited rate and to produce maximum inhibition are smaller, the same limiting curve is obtained.

It is of importance that all the partially inhibited pressure–time curves have at least a common tangent at the origin with the maximally inhibited curve; indeed the time at which the partially inhibited curve leaves the maximally inhibited one increases with inhibitor concentration. The behaviour shown in Fig. 1 may be interpreted on the view that the inhibitor both introduces an induction period and slows down the final rate

* Part IX, preceding paper.

† The Arrhenius parameters for these two substances have been briefly reported (*J. Chem. Phys.*, 1953, **21**, 178).

[1] Agius and Maccoll, *J.*, 1955, 973.

achieved by the chain reaction. This behaviour is again illustrated in Fig. 2, which shows the first-order plots for the runs illustrated in Fig. 1. With the exception of the uninhibited run, the initial first-order rate coefficients are the same but the deviation from the maximally inhibited line becomes less pronounced as the inhibitor concentration is increased. Although the facile explanation of this behaviour is that it is due to a trace of impurity in the inhibitor which is slowly consumed, this is not regarded as the correct explanation because the behaviour in the region of incomplete inhibition is characteristic of all olefinic inhibitors studied and of all bromides which undergo inhibition. The type of behaviour observed in the presence of inhibitors has one important consequence, that it enables the maximally inhibited reaction to be examined in the initial stages of the decomposition even though chain processes become operative in the later stages. Thus the first-order rate constant may be derived from the initial tangent to the log plot of a partially inhibited reaction. This has proved useful in studying the decomposition of compounds such as *iso*butyl bromide [2] for which the chain mechanism is so strongly developed that it is difficult to suppress it throughout the whole reaction.

FIG. 1. *Pressure–time curves, showing partial inhibition, at constant* p_0 *and with varying* p_1. (*a*) *Uninhibited*, (*b*) 250 *mm. of* isopentane, (*c*) 210 *mm. of propene*, (*d*) 267 *mm. of propene*, (*e*) 336 *mm. of propene*, (*f*) *maximally inhibited*, 350 *mm. of* cyclo*hexene*.

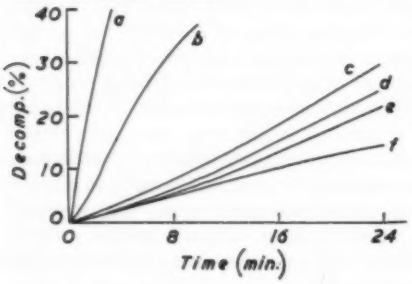
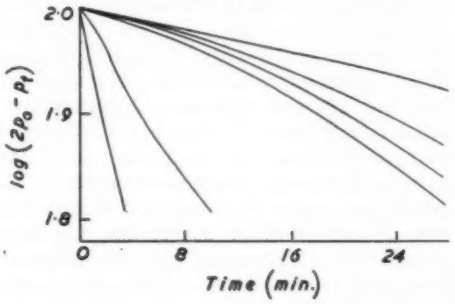


FIG. 2. *First-order plots for the runs illustrated in Fig.* 1.



The constancy of the initial rates in the presence of varying concentrations of inhibitor over a wide range is shown in Fig. 3. The initial rate of decomposition is independent of variations in partial pressure of *cyclo*hexene between 100 and 400 mm. It is not possible, without further work, to account for the broken portion of the curve, that is, to account for the rate as a function of time in the region of incomplete inhibition.

The efficiency of different inhibitors. The results shown in Fig. 3 also enable the important conclusion to be drawn that the *maximally* inhibited rate is independent of the nature of the olefinic inhibitor. However, as is evident from Fig. 1 and has been previously noted,[1] the concentration of propene required to produce maximal inhibition of the decomposition of *n*-propyl bromide was too great to permit an extensive investigation of the residual reaction. The investigation of the process occurring at maximal inhibition for this and for other compounds was thus preceded by a limited investigation of other olefinic substances which were thought to be possible inhibitors. Green and Maccoll's work [3] on *cyclo*hexyl bromide showed *cyclo*hexene to be much more efficient than propene, as well as being stable at 300—400°. Other compounds studied were 2 : 4-dimethylpent-2-ene and *cyclo*pentadiene.

Owing to the complicated kinetics in the region of partial inhibition, the relative efficiencies of different inhibitors cannot be compared very precisely. Table 1 shows the approximate partial pressures of inhibitors which produce the same degree of inhibition

[2] Unpublished work.
[3] Green and Maccoll, *J.*, 1955, 2449.

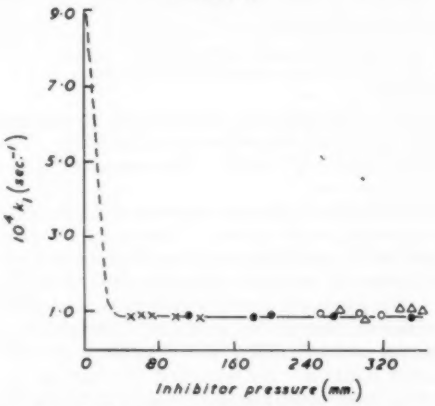
with a constant partial pressure of *n*-propyl bromide. Although *cyclo*pentadiene is more efficient than *cyclo*hexene, the tendency for this compound to dimerise vitiates its use for accurate work, except at very low partial pressures. *cyclo*Hexene is seen to be markedly more efficient than propene.

TABLE 1. *Efficiencies of inhibitors.*

Inhibitor	Propene	2 : 4-Dimethyl pent-2-ene	*cyclo*Hexene	*cyclo*Pentadiene
Pressure (mm.)	500	400	100	40

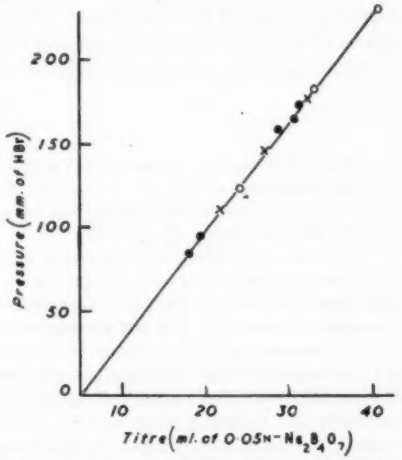
The efficiency of propene is assumed to be due to the stability of the allyl radical formed by abstraction of hydrogen by a bromine atom. A further structural factor might be the strength of the C–H bond concerned. By analogy with alkanes, it might be expected that a hydrogen attached to a tertiary carbon atom would be more readily abstracted, so 2 : 4-dimethylpent-2-ene, which possesses a tertiary allylic hydrogen

FIG. 3. *Maximal inhibition achieved by different inhibitors.*



● cyclo*Hexene*, ○ 2 : 4-*dimethylpent-2-ene*, △ *propene*, × cyclo*pentadiene*.

FIG. 4. *Analytical investigation of* n-*propyl bromide.*



The line is the calibration line, points being indicated as follows: ○ n-*propyl bromide alone*, × *in the presence of* cyclo*pentadiene*, ● *in the presence of* cyclo*hexene*.

atom, was examined: it was, however, not much more efficient than propene. The superiority of *cyclo*hexene over propene does not seem to be due to the fact that an allylic hydrogen atom attached to a secondary carbon atom is being attacked: rather must it arise from the cyclic nature of the inhibitor.

It is interesting that the relative ease of inhibition of chains in certain chloro-compounds, *e.g.*, 1 : 2-dichloroethane for which 2 mm. of propene suffice and for which *n*-hexane was quite effective, contrasts strongly with the present observations. Fig. 1 shows a pressure–time curve for the decomposition of *n*-propyl bromide in the presence of an appreciable amount of *iso*pentane. There is initially only a slight induction period, followed by a slight reduction in rate. The explanation of this lies in the large difference in activation energy of one of the chain-propagating steps:

$$\cdot C_nH_{2n}X \longrightarrow C_nH_{2n} + X\cdot$$

A lower limit for the activation energy of such a step can be obtained from thermochemical data.[4] The values in Table 2 are obtained from the heats of formation of the halides given

[4] Cf. Maccoll and Thomas, *J.*, 1955, 979.

by Mortimer, Pritchard, and Skinner,[5] and the heats of formation of the olefins are taken from an N.B.S. publication.[6] In addition, the primary C–H bond dissociation energy is

TABLE 2. *Activation energies (kcal./mole).*

Radical:	C_3H_6X	*n*-C_3H_6X	*iso*-C_3H_6X
X = Cl	21·6	22·9	25
X = Br	7·2	8·3	10·4

taken [7] to be 97 kcal./mole, as in ethane. The greater stability of the chloroalkyl radicals renders more probable the chain-ending process:

$$\cdot C_nH_{2n}Cl + \text{Inhibitor} \longrightarrow \text{End of chain}$$

which is believed to play very little part in the chain reactions of the bromides.

The results outlined in this section which bear upon the isolation of the unimolecular component of the reaction are as follows. First, the maximally inhibited rate is independent of the nature of the inhibitor. Secondly, it is independent, within wide limits, of the partial pressure of the inhibitor. If now it can be shown that the maximally inhibited rate is of the first order with respect to the bromide, it may be concluded that the unimolecular process is being investigated at maximal inhibition.

EXPERIMENTAL

n-Propyl Bromide.—Commercial *n*-propyl bromide was dried and fractionated, the middle fraction being redistilled and a fraction of constant b. p. and refractive index collected. The sample used for the kinetic work had b. p. 71·2°/763 mm., n_D^{25} 1·4317. Timmermans [8] gives b. p. 71·00°/760 mm., n_D^{25} 1·4318.

It was thought especially important to check that the rate of pressure increase was a measure of the rate of elimination of hydrogen bromide in the presence of inhibitor. Rather than use the technique described in Part II,[1] a method was used for the analytical measurements employing a vapour reservoir. Known amounts of pure hydrogen bromide were admitted into the reaction vessels and the pressure was measured. The hydrogen bromide was then condensed into an evacuated bulb which was sealed off and removed from the vacuum-line. The contents of the bulb were then analysed by breaking the tip under distilled water, washing out the contents, and titrating them against standard borax solution. By repeating this process for varying pressures of hydrogen bromide a graph was constructed relating pressure of hydrogen bromide to the titre of borax solution. After an experiment in which the maximally inhibited decomposition of *n*-propyl bromide was followed by pressure measurements, it was possible to remove the contents of the reaction vessel as described above, and determine the hydrogen bromide pressure in the reaction vessel immediately before its removal. The pressure determined in this way could thus be compared with that calculated from the expression, $p_{HBr} = P_t - p_0 - p_i$ where P_t is the total pressure and p_0 and p_i the initial pressure of the bromide and of the inhibitor respectively. Investigations at 380° are reported in Table 3. It is seen that the two methods agree to within about 1%, so it may be concluded that the stoicheiometry of the reaction even in the presence of an inhibitor may be represented by $C_3H_7Br \longrightarrow C_3H_6 + HBr$. Figure 4 shows the calibration line of pressure against ml. of 0·05N-borax, and the results of the investigation of *n*-propyl bromide.

In order to identify the maximally inhibited reaction with a unimolecular process, it must be demonstrated that the limiting rate is independent of the nature and, within certain limits, the concentration of the inhibitor. To this end, four olefinic inhibitors were employed, propene, 2 : 4-dimethylpent-2-ene, *cyclo*hexene, and *cyclo*pentadiene. With the first two compounds, inhibition was complete only for a very short period at the commencement of the reaction, so the rates could not be determined with the accuracy obtainable with *cyclo*hexene. The results

[5] Mortimer, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220.
[6] "Selected Values of the Properties of Hydrocarbons," Nat. Bur. Stand., Washington.
[7] Evans, *Discuss. Faraday Soc.*, 1951, **10**, 112.
[8] Timmermans, "Physicochemical Constants of Pure Organic Compounds," Elsevier, London, 1950.

TABLE 3.

p_{HBr} (press.)	p_{HBr} (anal.)	Reaction (%)	p_{HBr} (press.)	p_{HBr} (anal.)	Reaction (%)	p_{HBr} (press.)	p_{HBr} (anal.)	Reaction (%)
No inhibitor			With *cyclo*hexene			With *cyclo*pentadiene		
123	123	43·9	94	92	24·1	146	143	46·2
183	181	58·2	158	154	45·0	110	109	32·5
232	231	58·6	106	106	30·1	186	187	44·4
			83	84	23·5			
			165	165	45·3			
			173	169	37·5			
			104	105	22·0			

shown in Table 4 verify the independence of the maximally inhibited rate of the nature of the inhibitor (within the limits of experimental error) and of the concentration over a wide range. The typical log plot in Fig. 5 shows that the first-order rate holds until about 50% decomposition.

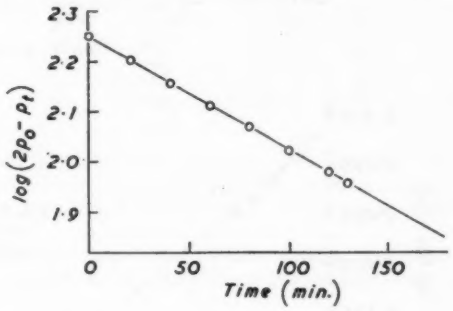


FIG. 5. *Typical first-order plot for the maximally inhibited reaction.*

The first-order nature of the reaction was proved for a wide range of initial pressures at 379°: the first-order rate constant is independent of initial pressure (Fig. 6) in a range 60—500 mm.

The homogeneity of the maximally inhibited reaction was verified by a number of runs done in a packed vessel, the surface : volume ratio being increased roughly five-fold. The

TABLE 4.

Temp.	p_0 (mm.)	p_1 (mm.)	10^3k_1 (sec.$^{-1}$)	10^5k_1 (sec.$^{-1}$; 380°) *	Temp.	p_0 (mm.)	p_1 (mm.)	10^3k_1 (sec.$^{-1}$)	10^5k_1 (sec.$^{-1}$; 380°) *
Propene					cyclo*Hexene*				
380·5	222	360	9·70	9·45	380	302	350	8·75	8·75
379	260	353	8·10	8·75	378·5	295	267	8·04	8·91
379	147	350	9·27	10·0	379	293	200	8·37	9·04
380	215	340	10·2	10·2	379	382	181	8·25	8·91
379·5	134	300	8·00	8·42	380	342	111	8·61	8·61
379	162	270	8·53	9·21	379	352	107	8·45	9·12
Mean 10^5k = 9·34 sec.$^{-1}$					Mean 10^5k = 9·04 sec.$^{-1}$				
2 : 4-*Dimethylpent-2-ene*					cyclo*Pentadiene*				
382	175	318	10·15	9·17	380	442	122	8·46	8·46
382	165	295	10·96	9·89	379·5	524	111	8·35	8·79
383	236	25	11·52	9·62	379·5	419	97	8·35	8·79
Mean 10^5k = 9·56 sec.$^{-1}$					379·3	342	92	8·16	8·59
					379	338	72	8·54	9·23
					378·5	286	60	8·19	9·08
					379	221	50	8·09	8·74
					Mean 10^5k = 8·8 sec.$^{-1}$				

* The correction is made by means of the Arrhenius plot, obtained from the results tabulated below.

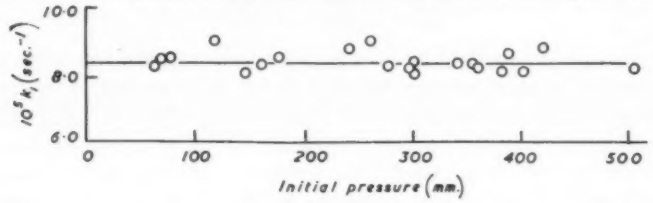
results in Table 5 are to be compared with values of $12·60 \times 10^{-5}$ sec.$^{-1}$ and $5·31 \times 10^{-5}$ sec.$^{-1}$ obtained by means of the Arrhenius equation from the results with an unpacked vessel.

Mean first-order rate constants derived from smoothed pressure–time curves, at 350—390°,

are shown in Table 6. Only the runs at 390° need comment in this series. As shown in Fig. 7 (a characteristic log plot), the reaction is characterised by a fast start. After an initial rapid period, however, it settles down to reasonable first-order behaviour. The most obvious explanation of this effect is initial incomplete inhibition. It must be emphasised, though, that this effect was not noticeable in the runs at the lower temperatures.

The Arrhenius equation, $k = 7{\cdot}94 \times 10^{12} \exp(-50{,}700/RT)$, was in excellent agreement with the experimental results.

FIG. 6. *Plot of the first-order rate constant as a function of initial pressure.*



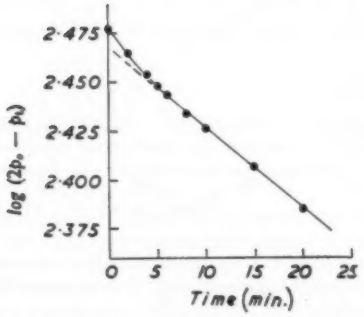


FIG. 7. *Log plot showing the fast start in the case of* n*-propyl bromide in the presence of* cyclo*hexene at* 390°.

n-*Butyl Bromide.*—This was obtained from commercial *n*-butyl bromide and also from commercial *n*-butyl alcohol. The material used in the kinetic runs had b. p. 103·3°/760 mm. (101·6°), n_D^{25} 1·4372 (1·4373), the values in parentheses being Timmerman's.[8] The kinetic behaviour of the two samples was identical.

TABLE 5.

Temp.	p_0 (mm.)	p_1 (mm.)	$10^5 k_1$ (sec.$^{-1}$)	Temp.	p_0 (mm.)	p_1 (mm.)	$10^5 k$ (sec.$^{-1}$)
385·5°	283	211	12·80	372°	305	229	5·78
385·5	254	258	12·05	372	284	184	5·83
385·5	231	261	12·40	372	194	225	5·44
385·5	194	149	12·40		Mean $10^5 k$ = 5·68 sec.$^{-1}$		
385·5	170	101	12·70				
385·5	162	220	12·60				
	Mean $10^5 k$ = 12·46 sec.$^{-1}$						

TABLE 6.

Temp.	350°	360°	370°	379°	390°
No. of runs	4	8	5	13	6
$10^5 k_1$ (sec.$^{-1}$)	1·42	2·72	4·96	8·42	16·7

A comparison of the decomposition calculated from pressure measurements on the basis of the equation, $C_4H_9Br \longrightarrow C_4H_8 + HBr$, with that obtained from a direct determination of the hydrogen bromide produced showed that the equation represented the stoicheiometry of the reaction, both in the presence and in the absence of *cyclo*hexene.

A number of runs at 392° were carried out in the presence of 2 : 4-dimethylpent-2-ene, *cyclo*pentadiene, and *cyclo*hexene, the inhibitor partial pressures being respectively in the ranges

150—250, 50—110, and 100—250 mm. The mean first-order constants were respectively 2·92, 2·68, and 2·73 × 10^{-4} sec.$^{-1}$. As in the case of *n*-propyl bromide, the rate constant with *cyclo*hexene is a little larger than with *cyclo*pentadiene, and smaller than that with 2 : 4-dimethylpent-2-ene. The low rate constant with *cyclo*pentadiene is probably explicable in terms of a dimerisation in the dead space of the apparatus. The experimental evidence demonstrates that the maximally inhibited rate is independent of the nature of the inhibitor. The remainder of the study of the maximally inhibited reaction was done with *cyclo*hexene as the inhibitor.

The lack of dependence of the maximally inhibited rate upon *cyclo*hexene pressure is shown in Table 7. This Table also justifies the use of first-order rate constants, which shows no variation with initial pressure in the range 35—405 mm. Four runs carried out at 371° and at 384°,

TABLE 7. *Inhibition by* cyclo*hexene at* 392°.

p_0 (mm.)	p_1 (mm.)	10^4k_1 (sec.$^{-1}$)	p_0 (mm.)	p_1 (mm.)	10^4k_1 (sec.$^{-1}$)	p_0 (mm.)	p_1 (mm.)	10^4k_1 (sec.$^{-1}$)
405	40	2·83	238	87	2·75	102	86	2·76
350	44	2·83	224	94	2·68	57·5	95	2·83
333	78	2·76	183	97	2·68	54·3	88	2·66
306	104	2·75	167	97	2·74	53	87	2·79
305	85	2·76	151	239	2·60	36·5	74	2·63
301	88	2·85	130	80	2·68	35	84	2·94
284	245	2·73	109	94	2·82	35	31	2·84
269	58	2·40						

and six at 400°, gave mean velocity constants of 8·50, 19·4, and 43·8 × 10^{-5} sec.$^{-1}$ respectively. The corresponding values in the unpacked vessel were respectively 8·06, 17·6, and 43·8 × 10^{-5} sec.$^{-1}$. In view of the five-fold increase in the surface : volume ratio, it may be concluded that the reaction is homogeneous.

The results from which the temperature variation of the velocity constant was derived are shown in Table 8. For the runs at 392°, only those for which the initial pressure was between

TABLE 8.

Temp.	371°	380°	392°	404·5°	418°
No. of runs	4	11	13	6	8
10^5k_1 (sec.$^{-1}$)	8·06	13·8	27·3	56·5	116

350 and 151 mm. were used in computing the mean, in order to ensure that the pressure range was comparable at all temperatures. The results in Table 8 were fitted to the equation

$$\log k_1 = 13{\cdot}18 - 50{,}900/2{\cdot}303RT$$

the experimental points lying very close to the theoretical line.

DISCUSSION

The maximally inhibited rates of pyrolysis of *n*-propyl and *n*-butyl bromide have been shown to satisfy the following criteria: (i) The first-order rate constants are independent of the nature of the olefinic inhibitor, of the inhibitor partial pressures over a wide range of pressure, and of the initial pressure of the bromide in the ranges 60—500 and 35—470 mm. respectively. (ii) The reactions are homogeneous. (iii) The rate constants satisfy the Arrhenius equations already given.

It is concluded that these rates pertain to the unimolecular elimination of hydrogen bromide. For *n*-propyl bromide, the parameters of the unimolecular reaction are in marked contrast with those of the uninhibited reaction, namely, $A \sim 10^{11}$ mole$^{-\frac{1}{2}}$ (c.c.)$^{\frac{1}{2}}$ sec.$^{-1}$ and $E \sim 34$ kcal./mole.

The parameters reported here are compared in Table 9 with those for the corresponding chlorides.[9]. R represents the ratio of the rates (Bu^n/Pr^n) at the temperature indicated, which was chosen so that the rate constants of the compounds were of the same order of magnitude. It will be seen that, despite the differences in the parameters of the Arrhenius equations, the rate ratios of the two compounds are very similar.

[9] Barton, Head, and Williams, *J.*, 1951, 2039.

TABLE 9.

	Chloride			Bromide		
Alkyl	$10^{-13}A$ (sec.$^{-1}$)	E (kcal./mole)	R (440°)	$10^{-13}A$ (sec.$^{-1}$)	E (kcal./mole)	R (370°)
Pr^n	2·83	55·0	—	0·79	50·7	—
Bu^s	10	57·0	1·3	1·51	50·9	1·5

After our work was completed, Blades and Murphy [10] reported results for *n*-propyl bromide in excellent agreement with it. They used toluene as carrier gas, in a flow technique similar to that developed by Szwarc.[11] In the temperature range 500—600° the rate was:

$$k_1 = 1{\cdot}0 \times 10^{13} \exp(-50{,}700/RT)$$

substantiating our values. This is the more impressive since the present work was done at about 100° lower. The fact that Blades and Murphy could detect no dibenzyl in their experiments is explicable in terms of the activation energies of the inhibited free-radical and unimolecular mechanisms: in the temperature range considered, the rate of the former would be relatively very small.

Recently, also, Semenov, Sergeev, and Kapralova [12] reported an investigation of the pyrolysis of *n*- and *iso*-propyl bromide. For the latter they found:

$$\log k_1 = 12{\cdot}74 - 47{,}000/2{\cdot}303RT$$

They confirmed the first-order, unimolecular character of the reaction, and the rate constants are in reasonable agreement with those given by Thomas and Maccoll [13] and Blades and Murphy.[14] However, for *n*-propyl bromide they reported that the reaction was of order 1·5, in agreement with Agius and Maccoll,[15] and that the rate constant could be represented by

$$\log k_{1\cdot5} = 9{\cdot}58 - 42{,}000/2{\cdot}303RT$$

with $k_{1\cdot5}$ in units of mm.$^{-\frac{1}{2}}$ sec.$^{-1}$. Changing to units of mole$^{-\frac{1}{2}}$ c.c.$^{\frac{1}{2}}$ sec.$^{-1}$, by conversion of the calculated rate constants at 300° and 350° into these units gives:

$$\log k_{1\cdot5} = 13{\cdot}62 - 42{,}700/2{\cdot}303RT$$

which is to be compared with Agius and Maccoll's equation namely

$$\log k_{1\cdot5} = 10{\cdot}86 - 33{,}800/2{\cdot}303RT$$

The temperature range investigated by Semenov *et al.* was 350—500°, which is to be compared with 300—380° studied by Agius and Maccoll. Although at first sight there appears to be a marked divergence between the rate equations, the maximum ratio of the rates in the overlapping temperature range is 2. As Semenov *et al.* point out, air was not rigorously excluded from Agius and Maccoll's apparatus, so possibly the coating on the walls of the vessel was oxidised, allowing heterogeneous catalysis. It should be pointed out that reproducibility in chain decompositions is very much more difficult to obtain than in reactions proceeding by a unimolecular mechanism.

The question as to the essential nature of the difference in pyrolytic behaviour of *n*- and *iso*-propyl bromide has been further discussed by Semenov.[16] Independently, he arrived at almost the same explanation as Maccoll and Thomas,[17] in terms of propagating

[10] Blades and Murphy, *J. Amer. Chem. Soc.*, 1952, **74**, 6219.
[11] Szwarc, *J. Chem. Phys.*, 1949, **17**, 432.
[12] Semenov, Sergeev, and Kapralova, *Doklady Akad. Nauk S.S.S.R.*, 1955, **105**, 301.
[13] Maccoll and Thomas, *J. Chem. Phys.*, 1951, **19**, 977; *J.*, 1955, 979.
[14] Blades and Murphy, *J. Amer. Chem. Soc.*, 1952, **74**, 6219.
[15] Agius and Maccoll, *J.*, 1955, 973.
[16] Semenov, "On a Number of Problems of Chain Reactions and Chemical Kinetics," Moscow, 1954.
[17] Thomas, Thesis, London, 1953; Maccoll and Thomas, *J.*, 1955, 979.

and stopping radicals. The only point of variance is the nature of the chain-ending step. Semenov favours $2CH_3{\cdot}CH_2{\cdot}CHBr{\cdot} \longrightarrow$ End of chain, whereas Maccoll and Thomas postulated $\cdot CH_2{\cdot}CH_2{\cdot}CH_2Br + Br \longrightarrow$ End of chain. Further work will be required before it is possible unambiguously to decide between the two mechanisms.

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1008. *Sesquiterpenoids. Part IX.* Stereospecificity in the Conversion of the Grouping* ·CO·ĊH·ĊH·CO· *into* ·CO·Ċ:Ċ·CO· *by Selenium Dioxide.*

By J. C. BANERJI, D. H. R. BARTON, and R. C. COOKSON.

Five stereoisomeric methyl 3 : 6-dioxoeudesmanoates have been prepared and their configurations determined. The relative rates of oxidation of these diketones by selenium dioxide to methyl 3 : 6-dioxoeudesm-4-enoate have been measured. The compounds with the 4 : 5-hydrogen atoms *cis* are oxidised faster than those with the *trans*-relationship. Oxidation rates for other diketones have been determined in support of this generalisation. The mechanism of these oxidations has been discussed further. Some of the results reported here have been the subject of a preliminary communication.[1]

THIS investigation is concerned with the preparation and reactivity of a series of compounds containing the saturated 1 : 4-dione grouping (I). The main objective of our work was to examine further the postulate[2] that the ease of their dehydrogenation to the unsaturated 1 : 4-dione system (II) by selenium dioxide was a function of the stereochemical relationship of the hydrogen atoms at positions 2 and 3. We describe first the preparation of some of these diketones derived from santonin.

(I) $-CO-\overset{|}{C}H-\overset{|}{C}H-CO- \longrightarrow -CO-\overset{|}{C}=\overset{|}{C}-CO-$ (II)

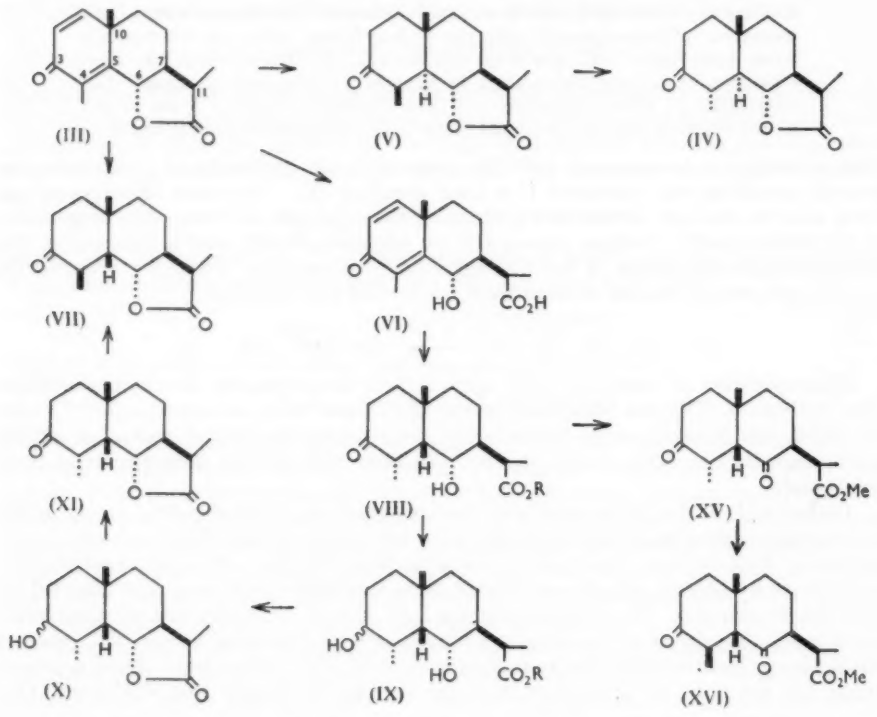
Hydrogenation of santonin[3] (III) affords three stereoisomeric tetrahydrosantonins. Two of these, α- (IV) and γ-tetrahydrosantonin (V), are based on *trans*-decalin[4,5] whilst the third, the β-isomer, more conveniently obtained by the hydrogenation of sodium santoninate (as VI), has a *cis*-ring fusion. We have confirmed the homogeneity of these compounds.

Cocker and McMurry[4] showed that the configuration of the 4-methyl group in the hydrogenation product of sodium santoninate was different from that in β-tetrahydrosantonin. This we have confirmed by showing that reduction of methyl β-tetrahydrosantoninate by lithium aluminium hydride gives a different triol from that afforded by β-tetrahydrosantonin. Now β-tetrahydrosantonin cannot be epimerised by perchloric–acetic acid. We therefore formulate it as the equatorial 4β-methyl isomer (VII), methyl tetrahydrosantoninate being the 4α-methyl compound (VIII; R = Me). These configurations are the opposite to those tentatively assigned by Cocker and McMurry.[4] Our

* Part VIII, *J.*, 1957, 150.

[1] Barton, *Experientia*, 1955, Suppl. II, p. 121.
[2] Barnes and Barton, *J.*, 1953, 1419.
[3] For stereochemistry see Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Abe and Sumi, *ibid.*, 1955, 253; Bruderer, Arigoni and Jeger, *Helv. Chim. Acta*, 1956, **39**, 858; Sumi, *Pharm. Bull.*, 1956, **4**, 158; further refs. are given in *Ann. Reports*, 1954, **51**, 208; 1955, **52**, 191.
[4] Cocker and McMurry, *J.*, 1956, 4549; and references there cited.
[5] Kovács, Herout, Horák, and Šorm, *Chem. Listy*, 1955, **49**, 1856; *Coll. Czech. Chem. Comm.*, 1956, **21**, 225; Tahara, *J. Org. Chem.*, 1956, **21**, 422; and references there cited.

views are supported by the fact that reduction of the ester (VIII; R = Me) with potassium borohydride gave a dihydroxy-ester (IX; R = Me) which, on hydrolysis to the acid and pyrolysis, furnished the hydroxy-lactone (X). Cautious oxidation of the latter gave a keto-lactone (XI), conveniently designated δ-tetrahydrosantonin, which was at once converted into β-tetrahydrosantonin (VII) on gentle treatment with perchloric–acetic acid. If one accepts a two-chair conformation for (VII) and (XI) then the $C_{(4)}$-configurations follow. The difficulty is to rationalise the preferred 4α-configuration of compounds (VIII; R = H or Me). The simplest explanation is that these have a boat-chair conformation (as XII), which is more stable than either of the two-chair conformations (XIII) and (XIV). The conformation (XIV) is obviously destabilised by the axial 4-methyl group interacting with the axial 7- and 9-hydrogen atoms. Conformation (XIII) must be destabilised by 1 : 3-interaction of the 4β-methyl group with the 6α-hydroxyl group: this is equivalent to the corresponding 1 : 3-diaxial interaction within a *cyclo*hexane ring. Although conformation (XII) is destabilised by the usual 1 : 2-interactions within a boat conformation the trigonal 3-carbonyl group minimises interactions with the axial 7- and 9-hydrogen atoms. An analogous situation has been discussed recently.[6] The destabilising 1 : 3-interaction in conformation (XIII) referred to above does not apply to the same



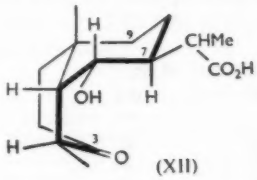
degree in β-tetrahydrosantonin (VII). This is because, according to models, the *trans*-fused γ-lactone ring pulls away the alkyl-oxygen atom from its interaction with the 4β-methyl group.

Cautious oxidation of methyl β-tetrahydrosantoninate (VIII; R = Me) gave a

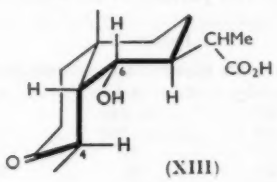
[6] Barton, Lewis, and McGhie, *J.*, 1957, 2907; see also Nace and Turner, *J. Amer. Chem. Soc.*, 953, **75**, 4063.

diketoester (XV) conveniently designated methyl β_1-3 : 6-dioxoeudesmanoate.* Reduction of the esters (VIII; R = Me) and (XV) with lithium aluminium hydride gave the same triol, confirming the assumption that inversion had not taken place. Nevertheless ester (XV) was very easily changed on chromatography over alumina or by piperidine into methyl β_2-3 : 6-dioxoeudesmanoate. This was shown to be compound (XVI), on the following evidence. First, the diketones (XV) and (XVI) gave different monoximes with pyridine–hydroxylamine hydrochloride. The 3-carbonyl group is, of course, much less hindered than the 6-group, so that the selective oximation must be at position 3. The oxime from ketone (XV) was stable under the conditions required to isomerise the parent (XV) to (XVI). The isomerisation must, therefore, involve at least inversion at $C_{(4)}$. Isomerisation of the diketone (XV) with triethylamine in deuterium oxide–dioxan gave an isomer (XVI) containing only one atom of deuterium. The rearrangement, therefore, in fact involves only the $C_{(4)}$-centre. The instability of the 4α-methyl group in compound (XV) compared with its stability in compound (VIII; R = Me) is comprehensible if one notes that oxidation of the 6α-hydroxyl to a ketone group removes in large part the destabilising 1 : 3-interaction in (XIII) referred to above. The stereochemisty of (XIII) then becomes the more stable arrangement as already implied in formula (XVI).

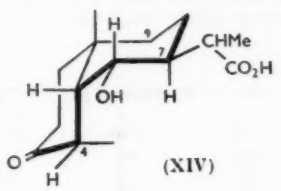
Further stereoisomers of methyl 3 : 6-dioxoeudesmanoate were obtained as follows. Dihydrosantonin [7] (XVII), best prepared by selective hydrogenation with Raney nickel in benzene,[8] was converted, by hydrolysis into the hydroxy-acid (XVIII), methylation, and oxidation with pyridine–chromium trioxide, into the unsaturated diketone (XIX). This was also obtained by oxidation of the diketone (XV) with selenium dioxide. Reduction with activated zinc dust in methanol afforded methyl γ-3 : 6-dioxoeudesmanoate (XX), readily converted by piperidine into the α-isomer (XXI). The latter compound was also



(XII)



(XIII)



(XIV)

obtained by reduction of the unsaturated diketone (XIX) with zinc dust and acetic acid. The assignment of configurations (XX) and (XXI) is based upon the concept of enol protonation from the less hindered α-side of the molecule,[9] upon the fact that (XXI) is the most stable of all the diketo-esters here reported (see below), and upon the certain identity of our ester (XXI), m. p. 79—81°, $[\alpha]_D$ −73°, with a diketo-ester, m. p. 81—82°, $[\alpha]_D$ −64°, prepared recently by Matsumura, Iwai, and Ohki [10] from α-tetrahydrosantonin (IV).

A fifth isomer, methyl ν-3 : 6-dioxoeudesmanoate, was isolated (after esterification) in about 10% yield from controlled alkali-treatment of the ester (XV) or (XVI) and by similar treatment of dihydrosantonin (XVII). Vigorous alkali-treatment converted the ν-diketo-ester into the α-isomer (XXI). The ν-diketo-ester is tentatively regarded as (XXII), with the diequatorial conformation (XXIII). The diminution of axial hydrogen–hydrogen interactions on the concave side of the molecule, as compared with (XVI) [conformation corresponding to (XIII)], would explain its greater stability.

The rates of oxidation of these and other diketones (I) by selenium dioxide were measured spectrophotometrically in acetic acid–dioxan at 65° (Table 1). For any pair of

* We are now adopting the convenient nomenclature proposed by Cocker and Cahn (*Chem. and Ind.*, 1955, 384; cf. Barton and de Mayo, *J.*, 1957, 150).

[7] Cusmano, *Annalen*, 1913, **400**, 332.
[8] Cf. Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[9] Zimmermann, *J. Org. Chem.*, 1955, **20**, 549; *J. Amer. Chem. Soc.*, 1956, **78**, 1168.
[10] Matsumura, Iwai, and Ohki, *J. Pharm. Soc. Japan*, 1955, **75**, 1043.

stereoisomeric ketones, that with the *cis*-configuration of eliminated hydrogen atoms is oxidised faster than that with the *trans*-arrangement. With one exception *all* the *cis*-compounds studied are oxidised faster than the *trans*-compounds. These results support Barnes and Barton's empirical rule,[2] but do not, of course, disprove reaction through the enol *provided* that the *cis*-compounds enolise faster than their *trans*-isomers. In order to

TABLE 1.*

Compound	No.	Relative configuration	Hours required for x% oxidation: x = 20%	30%	40%	50%
Methyl α-3 : 6-dioxoeudesmanoate (XXI)	1	*trans*	(4% in 120 hr.)			
3β-Acetoxylanostane-7 : 11-dione	2	*trans*	(9% in 120 hr.)			
Methyl 3β-acetoxy-12 : 19-dioxo-18α-oleanan-28-oate	3	*trans*	(10% in 120 hr.)			
Methyl β_2-3 : 6-dioxoeudesmanoate (XVI)	4	*trans*	32	52	77	120
Methyl 3β-acetoxy-12 : 19-dioxo-18β-oleanan-28-oate	5	*cis*	31	62	115	—
3β-Acetoxyergost-22-ene-7 : 11-dione	6	*trans*	28	48	84	120
Methyl ρ-3 : 6-dioxoeudesmanoate (XXII)	7	*cis*	20	35	100	—
Methyl γ-3 : 6-dioxoeudesmanoate (XX)	8	*cis*	8	12	18	25
Cholestane-3 : 6-dione	9	*cis*	4	7	11	18
Methyl β_1-3 : 6-dioxoeudesmanoate (XV)	10	*cis*	4	7	10	14
3β-Acetoxyeuphane-7 : 11-dione	11	*cis* † (?)	3	6	9	12

* See p. 5050 for details of conditions referred to in this and other Tables.
† See Knight and McGhie, *Chem. and Ind.*, 1953, 920; 1954, 24.

examine this the rates of bromination of most of the diketones of Table 1 were determined in acetic acid containing sodium acetate at 30° (Table 2). The tendency for the relative rates for the various diketones to run parallel in the two reactions supports the idea that

TABLE 2.

Compound no.	Hours required for consumption of x mol. of Br_2: x = 0·2	0·4	0·6	0·8
2	45	*ca.* 240	—	—
3	45	*ca.* 240	—	—
5	15	27	42	70
6	20	45	200	—
7	29	54	83	122
9	4	8	14	20
10	6	12	35	—
11	4	9	16	24

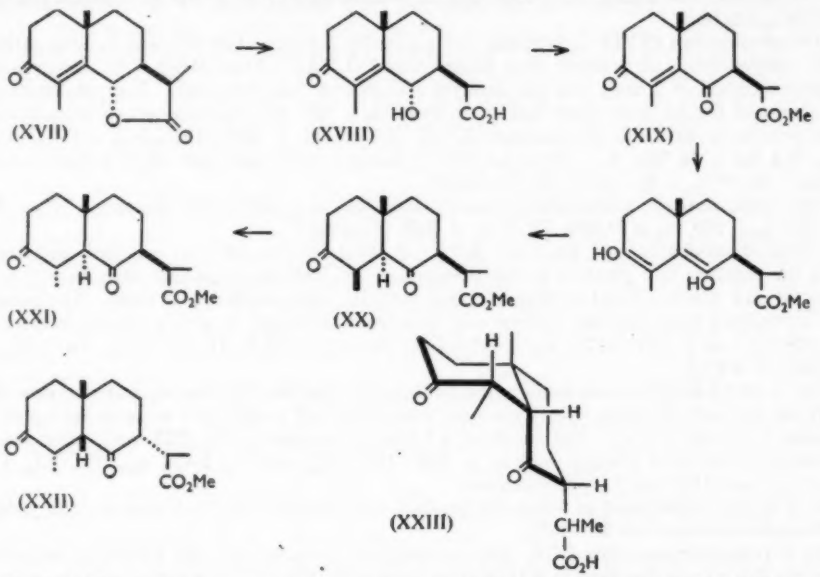
enolisation may be involved in oxidation by selenium dioxide as in bromination.

Now, the concentration of selenium dioxide might influence the rate partly by acid-catalysis of enolisation,[11] since (at least in aqueous solution) selenious acid (K_1 = $2{\cdot}4 \times 10^{-3}$) [12] is more than a hundred times stronger than acetic acid ($K = 1{\cdot}75 \times 10^{-5}$).[13] To estimate approximately the effect of selenious acid in catalysing enolisation, the rate of isomerisation of methyl β_1-3 : 6-dioxoeudesmanoate (XV) to the β_2-isomer (XVI) was measured polarimetrically at 65° in dioxan–acetic acid containing varying concentrations of chloroacetic acid ($K = 1{\cdot}36 \times 10^{-3}$) [14] which in water is about half as strong (see above) as selenious acid. The rates of isomerisation (Table 3) increased with the concentration of chloroacetic acid, but the rate of oxidation (Table 4) was much faster than that of isomerisation at equivalent acid concentration. This means either that the oxidation proceeds by a molecular mechanism or that the protonation of the enol of (XV) proceeds much faster to give back (XV) than to give (XVI). From the concept of proton-approach from the less hindered side of the enol [9] the latter is possible.

In order to avoid complications arising from the acidity of the selenious acid, further

[11] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 557.
[12] Hagisawa, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1939, **18**, 648; *Chem. Abs.*, 1940, **34**, 4965.
[13] Harned and Ehlers, *J. Amer. Chem. Soc.*, 1933, **55**, 652.
[14] Ives and Pryor, *J.*, 1955, 2104.

experiments on the β_1-diketo-ester were run at 30° in aqueous acetic acid buffered with sodium acetate. The rate of oxidation was reduced by the addition of sodium acetate



(Table 5). This is in agreement with a rate-determining attack by an electrophilic species upon an enol.

TABLE 3.

Hours reqd. for x% of isomerisation of 0·02M-diketone in dioxan–acetic acid containing chloroacetic acid

Molarity of chloroacetic acid	x = 20%	30%	40%	50%	60%	70%
0·0	13	22	33	48	69	100
0·4	7	12	17	22	28	39
0·8	4	7	9	12	15	19

TABLE 4.

Hours reqd. for x% of oxidation of 0·02M-diketone in dioxan–acetic acid containing 0·2M-selenium dioxide

x = 60%	80%	100%
2	5	26

TABLE 5.

Hours reqd. for x% of oxidation of 0·01M-diketone by 0·1M-selenium dioxide

Concn. (w/v) of sodium acetate dihydrate	x = 20%	30%	40%	50%	60%
2·5	8	16·5	25	34·5	44
5·0	11	20·5	30	44	84
10·0	19	37	74	—	—

In preliminary experiments in the buffered medium we showed that the oxidation rate was of the first order in both diketone and selenium dioxide. This behaviour is in contrast to bromination [11] and could be construed as support for the molecular mechanism.

It is clear then that, whilst the present experiments confirm the apparent stereospecificity of these selenium dioxide oxidations, they do not provide a final definition of the mechanism involved. Indeed, both possible mechanisms may be involved, molecular attack by the selenium dioxide residue being more important for the *cis*-diketones, whilst attack on the enol may be mandatory for the *trans*-isomers.

Experimental

Unless otherwise noted, ultraviolet spectra were measured for EtOH and optical rotations for $CHCl_3$ solutions.

Dihydrosantonin (XVII).—Santonin (2·0 g.) in dry benzene (100 ml.) was hydrogenated at room temperature and pressure over Raney nickel (1·5 g.). After about 1 hr. absorption of hydrogen ceased at 1 mol., and the catalyst and solvent were removed. Recrystallisation of the semisolid residue from ether–light petroleum (b. p. 60—80°) or from carbon tetrachloride–light petroleum gave dihydrosantonin (XVII) (1·7 g.), m. p. 101—102°, $[\alpha]_D$ +79° (*c* 1·42), $\lambda_{max.}$ 244 mμ (ε 14,700), $\nu_{max.}$ (in CCl_4) 1795 (γ-lactone), 1680 and 1628 cm.$^{-1}$ (αβ-unsaturated ketone): lit.,[10] m. p. 99°, $[\alpha]_D$ +75° (in EtOH).

The semicarbazone, recrystallised from ethanol, had m. p. 237—238° (decomp.), $[\alpha]_D$ +201° (*c* 1·12), $\lambda_{max.}$ 269 mμ (ε 27,800) [lit.,[10] m. p. 243° (decomp.)].

Tetrahydrosantonins.—(*a*) Santonin (4·0 g.) in ethyl acetate (120 ml.) was hydrogenated at room temperature and pressure in the presence of 1% palladium–calcium carbonate (1·8 g.). After 90 min. absorption of hydrogen ceased with the consumption of 2 mols. The product was crystallised from aqueous acetone and then from methanol, to give γ-tetrahydrosantonin (V) (628 mg.), m. p. 146—147°, $[\alpha]_D$ +64° (*c* 1·36) (Found: C, 71·8; H, 8·8. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·9%).

The α- and β-tetrahydrosantonin in the combined mother-liquors were separated as described by Wienhaus and Oettingen,[15] by hydrolysis with alkali and preferential re-lactonisation of the α-isomer with dilute acid. The resulting α-tetrahydrosantonin (IV) (773 mg.), after several recrystallisations from ethanol, had m. p. 154—155°, $[\alpha]_D$ +28° (*c* 1·45), $\nu_{max.}$ (in CCl_4) 1785 (γ-lactone) and 1710 cm.$^{-1}$ (*cyclo*hexanone).

In a typical experiment in which the product was treated with alkali directly, the yield of α-tetrahydrosantonin was 35—40%.

(*b*) β-Tetrahydrosantonin (VII) was conveniently obtained by the following procedure. Santonin (5·0 g.) was dissolved in 0·1N-sodium hydroxide (250 ml.) by warming and the solution was then hydrogenated at room temperature and pressure over Adams catalyst (0·5 g.). After 3 hr. absorption of hydrogen ceased with the uptake of 2 mols. The filtered solution was brought to pH 3 with dilute sulphuric acid and then heated on a steam-bath for ½ hr., to lactonise the easily lactonised acids. The cooled solution was extracted with ether, which was washed with 5% aqueous sodium carbonate till neutral. The carbonate layers were acidified and extracted with ether. After treatment with diazomethane the product crystallised from acetone–light petroleum (b. p. 60—80°), giving methyl β-tetrahydrosantoninate (VIII; R = Me) (3·47 g.), m. p. 158—160°, $[\alpha]_D$ +26° (*c* 1·49), $\lambda_{max.}$ 274 mμ (ε 24) (Found: C, 68·3; H, 9·2. Calc. for $C_{16}H_{24}O_4$: C, 68·05; H, 9·3%).

A sample of methyl β-tetrahydrosantoninate, m. p. 161—161·5°, $[\alpha]_D$ +26°, was separated into eleven fractions by chromatography on silica gel in 1 : 9 ether–benzene. All fractions had the same m. p. and rotation (±1°) as the original sample. The first and the last fraction, and intermediate fractions, showed no depression in mixed m. p.

The neutral material in the original ether extract that had been washed with sodium carbonate crystallised from aqueous methanol. The resulting α-tetrahydrosantonin (IV) (240 mg.), recrystallised from ethanol, had m. p. 153—155°, $[\alpha]_D$ +28° (*c* 1·42).

Hydrolysis of the methyl ester gave β-tetrahydrosantoninic acid (VIII; R = H), which formed crystals from acetone–light petroleum (b. p. 60—80°) with m. p. 193—194° (heated from 170°) and $[\alpha]_D$ +12° (*c* 2·00). The acid (80 mg.) was heated at 200°/16 mm. for 10 min. A solution of the product in ether was washed with 5% aqueous sodium carbonate, the ether was evaporated, and the product recrystallised from ether–light petroleum (b. p. 40—60°). β-Tetrahydrosantonin (VII) melted at 89—90°, resolidified, and melted again at 100—102°, and had $[\alpha]_D$ +7° (*c* 1·11), $\nu_{max.}$ (in CCl_4) 1785 (γ-lactone) and 1718 cm.$^{-1}$ (*cyclo*hexanone).

β-Tetrahydrosantonin (29·2 mg.) in acetic acid (3·0 ml.) was treated with 70% perchloric acid (4 drops) overnight at room temperature. There was no change in rotation. The solution was heated on the steam-bath for 1 hr. (again no change in rotation) and then worked up in the usual way, to give back β-tetrahydrosantonin (m. p. and mixed m. p.).

(*c*) δ-Tetrahydrosantonin (XI) was prepared in the following way. Methyl β-tetrahydrosantoninate (see above; 360 mg.) in methanol (8·0 ml.) was treated with potassium borohydride

[15] Wienhaus and Oettingen, *Annalen*, 1913, **397**, 219.

(36 mg.) in water (2·0 ml.) and left at room temperature for 1 hr. Dilution with water, filtration, and crystallisation from acetone–light petroleum (b. p. 60—80°) gave *methyl* 3ξ : 6α-*dihydroxy*-4β : 5β : 6β(H)-*eudesmanoate* (IX) (225 mg.), m. p. 135—136°, $[\alpha]_D$ +17° (*c* 2·34), +11° (*c* 2·18 in MeOH) (Found: C, 67·7; H, 9·85. $C_{16}H_{28}O_4$ requires C, 67·55; H, 9·95%). This ester diol (375 mg.) was saponified by refluxing for 1 hr. with 5% potassium hydroxide in methanol (12 ml.) and water (8 ml.). The acidic product (350 mg.), without purification, was heated at 200—210°/1·5 mm. for 5 min., to give a glass (329 mg.). Crystallisation from acetone–light petroleum (b. p. 60—80°) gave 3ξ-hydroxy-4β : 5β : 6β(*H*)-eudesman-6 : 13-olide (X) (205 mg.), m. p. 156—157°, $[\alpha]_D$ +39° (*c* 1·46) (Found: C, 71·7; H, 9·65. Calc. for $C_{15}H_{24}O_3$: C, 71·4; H, 9·6%). For this compound Cocker and McMurry [4] recorded m. p. 153—154°, $[\alpha]_D$ +37°. Potassium dichromate (181 mg.) in acetic acid (8·0 ml.) and water (2·0 ml.) was added to a solution of this hydroxy-lactone (300 mg.) in acetic acid (10·0 ml.) at 20° and left at this temperature for 4 hr. Dilution with water, extraction into ether, and washing with saturated aqueous sodium hydrogen carbonate solution and finally with water gave, on evaporation *in vacuo* at room temperature, a solid residue (170 mg.). Crystallisation from acetone–light petroleum (b. p. 40—60°) at room temperature or lower gave three crops of unchanged starting material (m. p. and mixed m. p.). Crystallisation of the residue from ether at −80° afforded the desired δ-*tetrahydrosantonin* (XI) (71 mg.), m. p. (plates) 119—120°, depressed on admixture with β-tetrahydrosantonin, $[\alpha]_D$ −30° (*c* 1·36 and 1·08 in EtOH), $\nu_{max.}$ (in Nujol) 1765 (γ-lactone) and 1705 cm.$^{-1}$ (*cyclo*hexanone) (Found: C, 72·1; H, 8·9. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). The infrared spectra of δ- and β-tetrahydrosantonins were different in the " finger-print " region. δ-Tetrahydrosantonin (28 mg.) was treated with perchloric acid, as described above for β-tetrahydrosantonin. The rotation at once changed at room temperature to $[\alpha]_D$ +15° (*c* 2·79 in acetic acid), identical with that of β-tetrahydrosantonin in the same solvent. Working up as above gave β-tetrahydrosantonin (23·6 mg.), identified by m. p., mixed m. p. and rotation {$[\alpha]_D$ +10° (*c*, 0·99 in EtOH)}.

The action of perchloric–acetic acid on 3ξ-hydroxy-4β : 5β : 6β(H)-eudesman-6 : 13-olide was also investigated. During 11 hr. at room temperature the rotation changed from +50° to +96°. Working up the acetic acid solution gave the corresponding acetate, identified with an authentic specimen (prepared by acetylation with pyridine–acetic anhydride overnight at room temperature) by m. p., mixed m. p., and rotation. The authentic specimen had m. p. 153—154°, $[\alpha]_D$ +72° (*c* 1·45), +92° (*c* 1·16 in acetic acid), in agreement with constants {m. p. 151—152°, $[\alpha]_D$ +71° (*c* 0·9)} recorded by Cocker and McMurry.[4]

(*d*) The conversion of γ- into α-tetrahydrosantonin was effected as follows. The γ-isomer (80 mg.) was dissolved in N-potassium hydroxide (2 ml.) on a steam-bath in 30 min. After acidification and a further 30 minutes' heating the solution was cooled. Recrystallisation of the precipitate from ethanol yielded α-tetrahydrosantonin (IV) (25 mg.), m. p. and mixed m. p. 153—154°, $[\alpha]_D$ +27° (*c* 1·05).

Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV).—Methyl β-tetrahydrosantoninate (VIII; R = Me) (1·5 g.) in acetic acid (3 ml.) and benzene (3 ml.) was treated with sodium dichromate dihydrate (550 mg.) in acetic acid (5 ml.). After 12 hr. at room temperature the product was isolated with ether and crystallised from acetone–light petroleum (b. p. 60—80°). The β_1-*diketo-ester* (XV) (794 mg.) had m. p. 94—95°, $[\alpha]_D$ −63° (*c* 1·35) (Found, after sublimation: C, 68·9; H, 9·1. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

The *oxime*, prepared in pyridine at room temperature, separated from ethanol–ether in needles, m. p. 153—154°, $[\alpha]_D$ −112° (*c* 1·03) (Found: C, 65·3; H, 8·6; N, 4·9. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Methyl β_2-3 : 6-*Dioxoeudesmanoate* (XVI).—Chromatography of the β_1-diketo-ester (100 mg.) in benzene on untreated (alkaline) alumina and crystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave the β_2-*diketo-ester* (XVI) (82 mg.), m. p. 127—128°, $[\alpha]_D$ −141° (*c* 1·56) (Found: C, 68·1; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

Chromatography of the residue from the mother-liquors of the β_1-diketo-ester (above) gave the β_2-isomer (300 mg.), m. p. and mixed m. p. 125—126°, $[\alpha]_D$ −138° (*c* 1·02).

The β_2-diketo-ester was also made directly from methyl β-tetrahydrosantoninate in good yield, by carrying out the oxidation as above on the steam-bath.

The *monoxime*, prepared in pyridine at room temperature, crystallised from ethanol–ether, m. p. 164—165°, depressed on admixture with β_1-oxime (see above), $[\alpha]_D$ +12° (*c* 1·51) (Found: C, 65·0; H, 8·2; N, 5·0. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Action of Piperidine on Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV) *and its Oxime.*—Piperidine (0·2 ml.) was added to a solution of the β_1-diketo-ester (0·5 mmole) in dioxan (24·8 ml.). The solution was heated in a stoppered flask jacketed with methanol vapour (65°), and the change in rotation was followed. After 68 hr. isomerisation was complete ($[\alpha]_D$ $-61° \longrightarrow -138°$). The product was crystallised from acetone–light petroleum (b. p. 60—80°), to yield the β_2-diketo-ester (XVI) (95 mg.), identified by m. p., mixed m. p., and rotation.

Under identical conditions a solution of the β_1-diketo-ester monoxime maintained a constant rotation. After 72 hr. the solute was isolated; crystallisation from ethanol–ether gave the unchanged monoxime (92 mg.), identified by m. p., mixed m. p., and rotation. The β_1-oxime was stable also to alkaline alumina.

Isomerisation of Methyl β_1-3 : 6-*Dioxoeudesmanoate* (XV) *in Presence of Deuterium Oxide.*—All organic solvents, except " AnalaR " acetone, had been freshly distilled from sodium. Triethylamine (5 ml.) was added to a solution of the β_1-diketo-ester (XV) (1·4 g.) in 1 : 19 deuterium oxide–dioxan (80 ml.). The solution was heated in a stoppered flask at the temperature of refluxing methanol. After 72 hr. the rotation indicated 75% of isomerisation to the β_2-isomer, and the solvents were evaporated *in vacuo* to a crystalline residue. Part of this was removed and rapidly recrystallised from acetone–light petroleum (b. p. 60—80°), yielding crystals (*A*), m. p. and mixed m. p. with β_2-diketo-ester (XVI) 126—127°, $[\alpha]_D$ $-138°$ (*c* 1·53). The rest of the product (*B*) after exhaustive drying *in vacuo* had $[\alpha]_D$ $-122°$, indicating 88% of β_2-isomer.

The samples were analysed for deuterium by Dr. G. Eglinton and his associates by complete combustion and measurement of the intensity of the O–D stretching vibration in the resulting water. The results, expressed in atoms of deuterium per mole, were: *A* (recrystallised) 1·0, 1·0; *B* (not recrystallised) 1·3.

Methyl ν-3 : 6-*Dioxoeudesmanoate* (XXII).—(a) *Isomerisation of* β_2-*diketo-ester.* The β_2-diketo-ester (XVI) (500 mg.) was boiled for 2 hr. in 10% sodium hydroxide solution (5 ml.). The oily mixture of acids, extracted with chloroform from the acidified solution, was esterified with diazomethane. Crystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave the ν-*diketo-ester* (XXII) (50 mg.), m. p. 182—184°. After several recrystallisations the ester had m. p. 188—189°, $[\alpha]_D$ $+64°$ (*c* 1·36) (Found: C, 68·3; H, 8·70. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

(b) *Isomerisation of* β_1-*diketo-ester* (XV). The β_1-diketo-ester (1 g.), dissolved in the minimum amount of methanol, was mixed with potassium carbonate (5 g.) in 50% aqueous methanol (250 ml.). After 90 minutes' boiling the acidic product was esterified with diazomethane. Crystals (90 mg.) separated from acetone–light petroleum (b. p. 60—80°) and on recrystallisation had m. p. and mixed m. p. with the ν-diketo-ester 187—188°. The material in the mother-liquors was chromatographed on alumina. The first fractions eluted with benzene gave pure ν-diketo-ester (XXII) (30 mg.) after two recrystallisations. Later benzene fractions, on recrystallisation, yielded slightly impure β_2-diketo-ester (12 mg.), m. p. and mixed m. p. 118—122°, $[\alpha]_D$ $-129°$ (*c* 0·5).

(c) *Isomerisation of dihydrosantonin* (XVII). Dihydrosantonin (5·0 g.) was boiled in 5% aqueous potassium hydroxide (100 ml.) under nitrogen for 8 hr. After acidification to pH 3 the solution was heated on a steam-bath for 10 min. Separation of the product into neutral and acid fractions gave only a small amount of neutral fraction. The acid fraction was methylated with diazomethane and crystallised from acetone–light petroleum (b. p. 60—80°), to yield the ν-diketo-ester (XXII) (542 mg.), m. p. and mixed m. p. 186—188°.

Dihydrosantonin (500 mg.) in ethanol (20 ml.) and concentrated hydrochloric acid (1 ml.) were refluxed for 10 hr.; alkaline hydrolysis and esterification gave the ν-diketo-ester (35 mg.).

The ν-*diketo-ester monoxime*, prepared in pyridine at room temperature, separated from ethanol–ether in needles, m. p. 165—166°, $[\alpha]_D$ $-29°$ (*c* 0·92) (Found: C, 65·1; H, 8·8; N, 5·15. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·55; N, 4·75%).

Methyl 3 : 6-*Dioxoeudesm-4-enoate* (XIX).—(a) *Dehydrogenation of methyl* β_1-3 : 6-*dioxoeudesmanoate* (XV). The β_1-diketo-ester (3·1 g.) was boiled with selenium dioxide (2·6 g.) in acetic acid (80 ml.) for 90 min. The chloroform extract of the diluted mixture was washed with alkali and then water. The residue from evaporation of the chloroform was boiled with precipitated silver for 1 hr. The product was chromatographed on acid-washed alumina (130 g.) in 1 : 9 benzene–light petroleum (b. p. 40—60°). The earlier fractions (total 1·02 g.),

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with m. p. *ca.* 60° and $\lambda_{max.}$ 255 mμ (ε 10,500), were combined. Six recrystallisations from light petroleum (b. p. 60—80°) gave *methyl* 3 : 6-*dioxoeudesm*-4-*enoate* (XIX) as colourless needles, m. p. 64—64·5°, $[\alpha]_D$ +113° (*c* 1·64) (Found, on a sublimed sample: C, 69·0; H, 7·9. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%).

(b) *From dihydrosantonin* (XVII). Dihydrosantonin (1·0 g.) was dissolved in warm 0·1N-sodium hydroxide (100 ml.). The solution at 0° was brought to pH 2 with dilute sulphuric acid and immediately extracted with ether. The ethereal solution was methylated with diazomethane and then evaporated *in vacuo* at room temperature. The resulting *methyl dihydrosantoninate* crystallised from light petroleum (b. p. 60—80°) containing a trace of acetone as needles, m. p. 104—105°, $[\alpha]_D$ +149° (*c* 1·8) (Found: C, 68·2; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%). Heating the methyl ester at 70° *in vacuo* for 24 hr. gave back dihydrosantonin (m. p. and mixed m. p.).

Methyl dihydrosantoninate (150 mg.) was oxidised with chromic oxide (150 mg.) in pyridine (5 ml.). After 24 hr. at room temperature the product was crystallised from light petroleum (b. p. 60—80°) containing a trace of acetone, yielding the enedione (XIX) (80 mg.), m. p. and mixed m. p. 64·5°, $[\alpha]_D$ +112° (*c* 0·57), $\lambda_{max.}$ 255 mμ (ε 10,500) and (in $CHCl_3$) 305—306 mμ (ε 110).

Methyl γ-3 : 6-*Dioxoeudesmanoate* (XX).—The enedione ester (XIX) (250 mg.) was boiled in methanol (200 ml.) with activated zinc dust (4 g.). After 8 hr. the maximum at 255 mμ had disappeared, and the cooled solution was filtered through "filter-aid," and then evaporated to dryness in the cold *in vacuo*. A solution of the residue in ether was washed with water. The oil remaining on evaporation of the ether crystallised from light petroleum containing a trace of acetone, to furnish *methyl* γ-3 : 6-*dioxoeudesmanoate* (XX) (100 mg.), m. p. (blades) 101—102°, $[\alpha]_D$ −7° (*c* 1·23) (Found: C, 68·4; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·55; H, 8·65%).

Methyl α-3 : 6-*Dioxoeudesmanoate* (XXI).—(*a*) The γ-diketo-ester (XX) (50 mg.) in dioxan (19 ml.) containing piperidine (1 ml.) was heated in a stoppered flask jacketed with refluxing methanol. After 48 hr. the initial rotation (−7°) had fallen to a constant value (−60°). Chromatography of the product on alumina and elution with 1 : 9 ether–benzene led to the α-diketo-ester (XXI), crystallising from a small volume of light petroleum (b. p. 60—80°) in needles (19 mg.), m. p. 81—82°, $[\alpha]_D$ −64° (*c* 0·9).

(*b*) The ester (XIX) (100 mg.) and zinc dust (1 g.) were boiled in acetic acid (10 ml.) for 2 hr. The isolated methyl α-3 : 6-dioxoeudesmanoate (XXI) crystallised from light petroleum in needles (40 mg.), m. p. and mixed m. p. 80—81°, $[\alpha]_D$ −64° (*c* 0·72) (Found: C, 68·6; H, 7·8. Calc. for $C_{16}H_{24}O_4$: C, 68·55; H, 8·65%).

(*c*) The ν-diketo-ester (XXII) (184 mg.) in 0·1N-sodium methoxide in methanol (25 ml.) was heated at 65° (methanol-vapour bath). After about 19 hr. the rotation became constant (−63°); the isolated product was chromatographed on silica gel (12 g.). Ether–benzene (1 : 19) eluted material that yielded pure α-diketo-ester (XXI) (7 mg.), identified by mixed m. p. and rotation.

Reductions by Lithium Aluminium Hydride.—(a) α-*Tetrahydrosantonin* (IV). The lactone (1 g.) in ether (500 ml.) was boiled with an excess of lithium aluminium hydride for 12 hr. The resulting *triol* separated from light petroleum (b. p. 60—80°) in rhomb-shaped crystals (640 mg.), m. p. 138—139°, $[\alpha]_D$ +8° (*c* 0·79) (Found: C, 70·5; H, 10·6. $C_{15}H_{28}O_3$ requires C, 70·25; H, 11·0%).

(b) *Methyl* α-3 : 6-*dioxoeudesmanoate* (XXI). The diketo-ester (60 mg.) on reduction and two recrystallisations from light petroleum ether gave a *triol*, flaky crystals (12 mg.), m. p. 135—136° [depressed on admixture with the triol from α-tetrahydrosantonin (see above)], $[\alpha]_D$ +12° (*c* 0·6) (Found: C, 70·7; H, 11·1%).

(c) β-*Tetrahydrosantonin* (VII). Reduction of the lactone gave a triol, m. p. [from ethanol–light petroleum (b. p. 40—60°)] 223—224°, $[\alpha]_D$ −41° (*c* 1·96 in EtOH), in good agreement with the constants recorded for this compound (m. p. 220°, $[\alpha]_D$ −43° in MeOH) by Cocker and McMurry.[4]

(d) *Methyl* β-*tetrahydrosantoninate* (VIII; R = Me). The ester (200 mg.) was reduced as above. The *triol* crystallised from acetone–light petroleum (b. p. 60—80°) in needles (103 mg.), m. p. 120—121°, $[\alpha]_D$ −14° (*c* 1·00) (Found: C, 69·8; H, 11·3%).

(e) *Methyl* β_1-3 : 6-*dioxoeudesmanoate* (XV). The diketo-ester (250 mg.) gave recrystallised triol (195 mg.), m. p. and mixed m. p. with the above sample from (d) 120—121°, $[\alpha]_D$ −14° (*c* 1·12) (Found: C, 70·4; H, 10·9%).

Miscellaneous Diketones.—In general the required enediones and derived saturated derivatives were prepared by published methods and had the expected physical properties.

Rate Measurements.—(a) *General.* In all experiments the appropriate blanks were run at the same time. Since the criterion of oxidation adopted was the measurement of the appearance of the appropriate ene-1 : 4-dione chromophore it was necessary to show that this gives a true measure of the rate of consumption of the selenium dioxide. This was checked in the case of the diketone (XV) by the following experiments. The rate of oxidation was determined in buffered aqueous acetic acid consisting of sodium acetate trihydrate (25 g.) in water (100 ml.) and " AnalaR " acetic acid (400 ml.). A solution of the ester (XV) (140 mg.) in the buffer (40 ml.) was mixed with selenium dioxide in the same solvent (10 ml.; containing 55·5 g. of selenium dioxide per l.) at 30° and held at this temperature. Periodically portions (5 ml.) were withdrawn, diluted with water (200 ml.), and acidified (20 ml. of 6N-hydrochloric acid). 0·05N-Sodium thiosulphate was then added, care being taken that the excess of this reagent did not exceed the recommended limit.[16] The excess of thiosulphate was then titrated with iodine. This gave the rate of consumption of selenium dioxide. The rate of development of the enedione chromophore (see XVIII) was measured on the Unicam S.P. 500 spectrophotometer as usual. Typical results are shown in Table 6.

TABLE 6. *Oxidation of* 0·01M-*ester* (XV) *by* 0·1M-*selenium dioxide.*

Reaction time (hr.)	8	23	31	48	72
SeO_2 consumed (volumetric) (%)	9·2	16·7	20·7	30·0	37·0
Enedione (XVIII) produced (spectr.) (%)	16·1	36·0	39·3	55·7	59·2

(b) *Notes on Table* 1. The standard solution of selenium dioxide contained 11·0 g./l. in 99% acetic acid. This solution (5 ml.) was added to one of the diketone (0·05 mmole) in purified dioxan (20 ml.), and the mixture was heated in a stoppered flask, jacketed with the vapour of refluxing methanol (65°). Periodically 1 ml. of the mixture was withdrawn and diluted to 10 ml. with ethanol. The optical density (kept between 0·25 and 0·5 by choice of cell-thickness or dilution) of the resulting solution was then measured at the wavelength of the maximum of the expected enedione against an appropriate blank. The extent of reaction was calculated by using $\varepsilon_{max.}$ of the pure enedione measured in the same solvent.

(c) *Notes on Table* 2. Bromine (6 mmoles) in acetic acid–carbon tetrachloride (4 : 1 by vol.) was added to a solution of the diketone (1 mmole) and anhydrous sodium acetate (2 g.) in the same solvent, bringing the total volume to 200 ml. The reaction flasks and controls were protected from light and kept in a thermostat at 30°. The consumption of bromine was determined iodometrically.

(d) *Notes on Table* 3. Methyl β_1-3 : 6-dioxoeudesmanoate (XV) (1 mmole) was dissolved in dioxan containing chloroacetic acid (none, 20 or 40 mmoles). 98% Acetic acid (10 ml.) was added, and the solution made up to 50 ml. with dioxan. The extent of isomerisation was determined by measurement of the optical rotation after various times of heating at 65°. Under the same conditions the rotation of the β_2-diketo-ester (XVI) scarcely changed.

(e) *Notes on Table* 4. The rate of development of the ene-1 : 4-dione chromophore was measured in the same mixture as used for work in Table 3, but containing selenium dioxide (10 mmoles) in place of chloroacetic acid.

(f) *Notes on Table* 5. The rate of oxidation by selenium dioxide was followed spectrophotometrically, as before, at 30°. The solvent was the buffered acetic acid mixture referred to under (a), but with variation in the concentration of sodium acetate.

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1009. *Reactions of the Phenylboron Chlorides and Bromides and the Chemistry of* n-*Butyl Phenylbromoboronite.*

By E. W. Abel, W. Gerrard, and M. F. Lappert.

Diphenylboron halides (Cl, Br) do not react with ethers or sodium. Phenylboron dibromide with *n*-butyl *tert.*-butyl ether gives *n*-butyl phenylbromoboronite, Ph·BBr·OBu^n, and *tert.*- and *iso*-butyl bromide. Reaction of diphenylboron halides with boron halides, hydrogen bromide, or bromine at high temperature and pressure causes cleavage of boron–carbon bonds. The properties of *n*-butyl phenylbromoboronite, the first stable alkoxyboron bromide, are described.

The present paper extends work on the preparation [1,2,3,4] and properties [5,6,7,8] of phenylboron halides, $PhBX_2$ and Ph_2BX (X = Cl, Br) to reactions involving replacement of halogen or phenyl (B–C cleavage).

Phenylboron dibromide, previously prepared in low yield from diphenylmercury and boron tribromide,[8] has now been prepared in good yield from phenylboron oxide and boron tribromide.

Phenylboron bromides, like the chlorides,[2] are readily hydrolysed: $Ph{\cdot}BBr_2 + H_2O \longrightarrow Ph{\cdot}BO + 2HBr$; or $2Ph_2B{\cdot}Br + H_2O \longrightarrow (Ph_2B)_2O + 2HBr$.

Alcoholysis of phenylboron chlorides has previously been reported.[9,10] Phenylboron dibromide with butan-1-ol yielded *n*-butyl phenylbromoboronite ($Ph{\cdot}BBr_2 + Bu^nOH \longrightarrow Ph{\cdot}BBr{\cdot}OBu^n + HBr$) or di-*n*-butyl phenylboronate [$Ph{\cdot}BBr_2 + 2Bu^nOH \longrightarrow Ph{\cdot}B(OBu^n)_2 + 2HBr$]. Diphenylboron bromide with (−)-1-methylheptanol gave (+)-1-methylheptyl, diphenylborate, $Ph_2B{\cdot}OR$ with retention of configuration.[4]

Diphenylboron halides did not react with ethers, whereas phenylboron dibromide cleaved *n*-butyl *tert.*-butyl ether at room temperature, being thus more reactive than phenylboron dichloride:[6]

$$Ph{\cdot}BBr_2 + ROR' \longrightarrow Ph{\cdot}BBr{\cdot}OR' + RBr$$

It appears that for a boron halide to cause C–O fission of an ether it is necessary that it be a tri- or di-halide. Thus boron trihalides and alkyl dichloroboronites [11] $RO{\cdot}BCl_2$ cleave most ethers at −80° or at lower temperatures, phenylboron dichloride [6] reacts at about 150°, and dialkyl chloroboronates [11] $(RO)_2BCl$ and alkyl arylchloroboronites [5] $Ar{\cdot}BCl{\cdot}OR$ are generally unreactive. The products from phenylboron dibromide were *n*-butyl phenylbromoboronite and a mixture of *tert.*- and *iso*-butyl bromide. The direction of fission is in accord with an S_Ni mechanism,[6,12] involving carbonium-ion formation from the more electron-releasing of the two alkyl groups in the ether. This is further supported by the observed molecular rearrangement, although rearrangement of *tert.*-butyl to *iso*butyl compounds is not common.

Diphenylboron halides did not react with metallic sodium, possibly owing to steric hindrance to the formation of the expected tetraphenyldiboron, $(Ph_2B)_2$.

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[2] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.
[3] Mikhailov and Fedotov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1956, 375.
[4] Abel, Gerrard, and Lappert, *J.*, 1957, 3833.
[5] Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 2872.
[6] *Idem*, *J.*, 1957, 2893.
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[8] Michaelis and Richter, *Annalen*, 1901, **315**, 216.
[9] Brindley, Gerrard, and Lappert, *J.*, 1956, 1540.
[10] Abel, Gerrard, and Lappert, *J.*, 1957, 112.
[11] Lappert, *Chem. Rev.*, 1956, **56**, 959.
[12] Martin, *ibid.*, 1948, **42**, 581.

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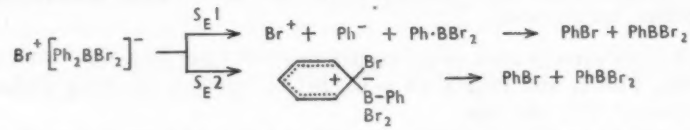
Diphenylboron halides underwent mutual replacement with boron trihalides at 200° under pressure: $Ph_2B{\cdot}X + BX_3 \longrightarrow 2Ph{\cdot}BX_2$.

Diphenylboron bromide with hydrogen bromide at 100° under pressure gave benzene and boron tribromide (isolated as its pyridine complex [12]). The boron–carbon bonds in diphenylboron bromide were also cleaved by bromine at 200° under pressure, yielding bromobenzene and boron tribromide, with small amounts of polybromobenzenes (formed by bromination of bromobenzene or of diphenylboron bromide).

We interpret the last three reactions as involving initial nucleophilic attachment of the appropriate reagent to the diphenylboron halide to form complexes, $H^+[Ph_2BBr_2]^-$, $Br^+[Ph_2BBr_2]^-$, and $[BX_2]^+[Ph_2BX_2]^-$. Subsequent transformation may then involve either of two mechanisms, exemplified as follows:



n-*Butyl Phenylbromoboronite.*—This compound (prepared as above) is the first bromoboronite, R·BBr·OR′ (R and R′ = alkyl or aryl) to be prepared: corresponding fluoro- and chloro-compounds are known.[1,9,13] It is also the first alkoxyboron bromide: dialkyl bromoboronates $(RO)_2B{\cdot}Br$ and alkyl dibromoboronites $RO{\cdot}BBr_2$ are unknown;[11] recent attempts to prepare the methyl homologues have failed.[14]

n-Butyl phenylbromoboronite is a colourless liquid at room temperature, but crystalline at −80°. It fumes in air with evolution of hydrogen bromide and reacts with *n*-butanol: $Ph{\cdot}BBr{\cdot}OBu^n + Bu^nOH \longrightarrow Ph{\cdot}B(OBu^n)_2 + HBr$. Thermally it is fairly stable; after 8 hr. at 100° only 10% of decomposition (to phenylboron oxide and butyl bromide) had occurred, but this was complete after 2 hr. at 200°. Its chloro-analogue underwent negligible decomposition under these conditions.[9] This is to be expected from the mechanism, involving rate-determining boron–halogen fission, proposed for decomposition of phenylchloroboronites.[9] *n*-Butyl phenylbromoboronite, like its chloro-analogue,[9] was catalytically and exothermally decomposed at 20° (as above) by a trace of anhydrous ferric chloride.

Experimental

General Procedures.—Dry hydrogen bromide was prepared by Gerrard's method [15] and condensed at −80°. Diphenylboron chloride was obtained by the method of Abel, Dandegaonker, Gerrard, and Lappert [2] and diphenylboron bromide as described by us previously.[4] Analytical methods were those used in earlier investigations.[4,6]

Interaction of Boron Tribromide and Phenylboronic Anhydride.—The tribromide (24·1 g.) was added to the anhydride (10·0 g.) in methylene dichloride (100 c.c.) at −80°. After 25 hr. at 20° volatile matter and solvent were removed (20°/15 mm.) to afford phenylboron dibromide (12·7 g., 53·6%), b. p. 80°/8 mm. (Found: B, 4·5; Br, 64·7. Calc. for $C_6H_5BBr_2$: B, 4·4; Br, 64·5%). Ether-extraction of the residue gave phenylboronic anhydride (3·82 g.) (Found: B, 10·1. Calc. for C_6H_5OB: B, 10·4%). A sample after recrystallisation (as phenylboronic acid from water, and subsequent dehydration) had m. p. 216°. After allowance for recovered anhydride the yield of dibromide was 85%.

Hydrolysis of Phenylboron Dibromide.—Water (0·135 g.) in *n*-pentane (30 c.c.) was added to phenylboron dibromide (1·86 g.) in *n*-pentane (20 c.c.). Hydrogen bromide (97%) was trapped in potassium hydroxide. Removal of solvent at 0·2 mm. left phenylboronic anhydride (0·75 g., 95%) (Found: B, 10·4%), which after recrystallization, as phenylboronic acid from hot water, and dehydration (120°/5 hr.) had m. p. 218°.

Hydrolysis of Diphenylboron Bromide.—Water (0·0397 g.) in ether (10 c.c.) was added to

[13] Mikhailov and Kostroma, *Izvest. Akad. Nauk, S.S.S.R., Otdel. khim. Nauk*, 1956, **376**.
[14] Goubeau, Becher, and Griffel, *Z. anorg. Chem.*, 1956, **282**, 86.
[15] Gerrard, *Research*, 1954, **7**, S20.

diphenylboron bromide (1·08 g.). Hydrogen bromide (96%) was trapped in potassium hydroxide. Removal of solvent at 10 mm. left crystalline diphenylboronous anhydride (0·74 g., 97%), m. p. 115° (Found: B, 6·3. Calc. for $C_{24}H_{20}OB_2$: B, 6·3%).

*Interaction of Phenylboron Dibromide and Butan-*1*-ol.*—Butan-1-ol (1·19 g., 1 mol.) in *n*-pentane (10 c.c.) was added to phenylboron dibromide (4·00 g., 1 mol.) in *n*-pentane (15 c.c.). Hydrogen bromide (1·19 g., 91%) was trapped in potassium hydroxide. After removal of solvent at 10 mm., distillation yielded n-*butyl phenylbromoboronite* (3·69 g., 95%), b. p. 67°/0·15 mm., d_4^{20} 1·233, n_D^{20} 1·5166 (Found: C, 50·3; H, 5·8; Br, 33·4; B, 4·6. $C_{10}H_{14}OBrB$ requires C, 49·8; H, 5·8; Br, 33·4; B, 4·5%).

Use of two mols. of butanol gave hydrogen bromide (91%) and di-*n*-butyl phenylboronate (2·72 g., 84%), b. p. 87°/0·01 mm., n_D^{20} 1·4748 (Found: B, 4·5. Calc. for $C_{14}H_{23}O_2B$: B, 4·6%).

Alcoholysis of Diphenylboron Bromide.—(−)-Octan-2-ol (2·05 g.; α_D^{20} −6·96°) in *n*-pentane (10 c.c.) was added to diphenylboron bromide (3·86 g.) in *n*-pentane (20 c.c.) at −80°, whereafter the mixture was warmed to 20°. Hydrogen bromide (1·26 g., 96%) was trapped in sodium hydroxide. Solvent was removed at 10 mm., to give (+)-1-methylheptyl diphenylboronite (4·43 g., 96%), n_D^{20} 1·5196, α_D^{20} +4·06° (Found: B, 3·7. Calc. for $C_{20}H_{27}OB$: B, 3·7%).

Interaction of Phenylboron Dibromide and n-*Butyl* tert.-*Butyl Ether.*—The ether (1·46 g.) was added to the dibromide (2·74 g.); heat was evolved. After 50 hr. at 20°, volatile matter (1·47 g.) was removed at 0·2 mm. and trapped at −80°. A gas-phase chromatogram of the condensate showed the presence of *tert.*- (60%), *iso*- (32%), and *n*-butyl bromide (4%) and *n*-butyl *tert.*-butyl ether (4%). The liquid residue afforded *n*-butyl phenylbromoboronite (2·24 g., 82%), b. p. 74°/0·6 mm., n_D^{20} 1·5173 (Found: Br, 33·7; B, 4·5%).

Interaction of Diphenylboron Halide and Boron Trihalide.—Diphenylboron chloride (9·56 g.) and boron trichloride (5·60 g.) were heated in a heavy-walled glass tube at 200° for 75 hr. Phenylboron dichloride (13·65 g., 90%), b. p. 58°/9 mm., n_D^{20} 1·5440 (Found: Cl, 44·4; B, 7·0. Calc. for $C_6H_5Cl_2B$: Cl, 44·6; B, 6·9%), and diphenylboron chloride (0·47 g.) (Found: Cl, 17·2; B, 5·5. Calc. for $C_{12}H_{10}ClB$: Cl, 17·7; B, 5·4%) were obtained. Boron trichloride (0·35 g.) was trapped in potassium hydroxide during the distillation.

Diphenylboron bromide (14·24 g.) and boron tribromide (14·65 g.) were similarly heated at 200° for 10 hr. Crystalline phenylboron dibromide (18·18 g., 69%), b. p. 59°/0·5 mm. (Found: Br, 64·1; B, 4·5%), was obtained, leaving a semisolid residue (4·32 g.). Boron tribromide (5·60 g.), n_D^{20} 1·5207 (Found: Br, 95·0; B, 4·2. Calc. for BBr_3: Br, 95·7; B, 4·3%), was trapped at −80°.

Interaction of Diphenylboron Bromide and Hydrogen Bromide.—Diphenylboron bromide (2·11 g.) and liquid hydrogen bromide (1·40 g.) were sealed in a heavy-walled glass tube at −80° and then heated at 100° for 30 hr. The tube was opened at −80°; the contents were condensed from 20°/10 mm. into a trap at −80°. To the condensate pyridine (0·68 g.) was added in 15 min. Benzene (1·30 g., 96%), n_D^{20} 1·5010, b. p. 79°, was removed at 20°/15 mm. and trapped at −80°. The crystalline residue was washed with *n*-pentane and water, and dried to constant weight at 20°/0·05 mm. Boron tribromide–pyridine (3·56 g., 85%) (Found: Py, 23·4; Br, 72·7. Calc. for BBr_3,C_5H_5N: C_5H_5N, 23·9; Br, 72·9%), m. p. 125—128°, was obtained.

Interaction of Diphenylboron Bromide and Bromine.—Diphenylboron bromide (8·65 g.) and bromine (11·32 g.) were heated at 200° for 15 hr. under pressure. Boron tribromide (8·08 g., 91%), b. p. 88°, n_D^{20} 1·5235 (Found: Br, 94·9; B, 4·2%), was removed at 20°/15 mm. and trapped at −80°. The remaining liquid yielded bromobenzene (8·03 g., 72%), b. p. 54°/16 mm., n_D^{20} 1·5613 (identified also by its infrared spectrum). A residue (3·43 g.) gave pale yellow crystals (probably a mixture of polybromobenzenes) on recrystallization from alcohol.

Alcoholysis of n-*Butyl Phenylbromoboronite.*—Butan-1-ol (1·14 g.) in *n*-pentane (10 c.c.) was added to the boronite (3·73 g.) in *n*-pentane (10 c.c.). Hydrogen bromide (1·18 g., 95%) was trapped in sodium hydroxide. After removal of solvent at 0·3 mm., di-*n*-butyl phenylboronate (3·38 g., 93%), b. p. 94°/0·4 mm., n_D^{20} 1·4743 (Found: B, 4·6%), was obtained.

Catalytic Decomposition of n-*Butyl Phenylbromoboronite.*—Ferric chloride (0·01 g.) was added to *n*-butyl phenylbromoboronite (1·65 g.) at −80°. Warming to 20° caused an exothermal reaction. *n*-Butyl bromide (0·92 g., 97%), n_D^{20} 1·4394 (Found: Br, 57·6. Calc. for C_4H_9Br: Br, 58·4%), was removed at 10 mm. and trapped at −80°. Phenylboronic anhydride (0·73 g. Required, 0·71 g.) (Found: B, 10·4%) remained. A sample of the anhydride after recrystallization, as phenylboronic acid from hot water, and subsequent dehydration had m. p. 216°.

Thermal Stability of n-*Butyl Phenylbromoboronite.*—The stability of the ester was determined by heating small samples in sealed tubes, and analysing acidimetrically the contents after stated times, by hydrolysis in cold water. Extent of reaction is indicated by the lowering of ratio of easily hydrolysed bromine to boron. Results are tabulated.

Temp.	100°	100°	100°	200°	200°	200°	200°
Time (hr.)	1	5	8	0·25	0·5	1	2
Decompn. (%)	2·7	6·4	10	11·2	30·2	65·5	97

Addition of Ethers to Diphenylboron Bromide and Chloride.—Diphenylboron bromide and chloride were recovered quantitatively after an equimolecular mixture of each halide severally and diethyl ether had been at 20° for 2 hr. Recovery was the same in each case after admixture with allyl phenyl ether.

Addition of Diphenylboron Bromide and Chloride to Sodium.—The halide (about 5 g.) in *n*-pentane (20 c.c.) was added to sodium wire (10 g.) in *n*-pentane (50 c.c.). After 50 hr. at 20° the sodium was filtered off; removal of solvent left diphenylboron halide, which on distillation left only a small solid residue.

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1010. *Excited States of Glyoxal.*

By GERALD W. KING.

The (0–0) bands in the absorption spectra of glyoxal and dideuteroglyoxal, at approximately 4550 Å, have been photographed with a 20 ft. Ebert grating spectrograph. A rotational analysis of their observed structure is suggested, according to which glyoxal has a planar, centrosymmetric *trans*-configuration in each electronic state of the transition and the excited state has A_u electronic symmetry. Assuming values for the C–H bond length and angle, we have obtained values for the ∠CCO and the sum of the C–C and C–O bond lengths for the vibronic states of the molecule concerned in the transition. The rough values for individual bond lengths deduced do not agree with the predictions of simple molecular-orbital theory concerning the dimensions of the excited state.

MONOMERIC glyoxal vapour possesses a system of weak, discrete absorption bands between 5000 Å and 3700 Å.[1,2] These appear diffuse towards shorter wavelengths. The spectrum has also been obtained in emission.[3,4] Brand [1] has suggested a convincing analysis of these bands, based on their appearance when photographed with use of a prism spectrograph of moderate resolving power.

There is little evidence as to the precise structure of the molecule in the ground state. Infrared [5] and electron-diffraction [6] indicate a planar, *trans*-configuration, of C_{2h} symmetry. On this assumption, the electron-diffraction measurements have given the following dimensions:

$$r_{CC} = 1{\cdot}47 \pm 0{\cdot}02 \text{ Å}; \; r_{CO} = 1{\cdot}20 \pm 0{\cdot}01 \text{ Å}; \; \angle CCO = 123 \pm 2°$$

[1] Brand, *Trans. Faraday Soc.*, 1954, **50**, 431.
[2] Thompson, *ibid.*, 1940, **36**, 988.
[3] *Idem, J. Chem. Phys.*, 1939, **7**, 855.
[4] Gaydon, *Trans. Faraday Soc.*, 1947, **43**, 36.
[5] Cole and Thompson, *Proc. Roy. Soc.*, 1949, *A*, **200**, 10.
[6] LuValle and Shomaker, *J. Amer. Chem. Soc.*, 1939, **61**, 3520.

with the assumed values $r_{CH} = 1{\cdot}09$ Å and $\angle CCH = 114°$. In addition, it is reasonable to assume that the ground state electronic configuration is ^1A_g, all the electrons being paired in orbitals of lowest energy. (*trans*-Glyoxal has the same symmetry classifications as has *trans*-acetylene; for tables showing the electronic and vibrational symmetry species, their direct products, and the overall symmetry classifications of the rotational energy levels, see ref. 7.)

Brand's analysis shows that, given a planar ground state of this symmetry, then the excited state of the electronic transition is also *trans*- and planar, with A_u symmetry. However this assignment largely depends upon the apparent polarisation of the transition moment of certain vibrational bands; that is, whether they are type A, B, or C bands polarised respectively along the *a*, *b*, or *c* momental axes of the molecule. In particular, there is one strong band (at 21,973 cm.$^{-1}$ in glyoxal and at 22,013 cm.$^{-1}$ in dideuteroglyoxal) which appears strongly both in absorption and emission and is very probably the (0–0) origin band of the electronic transition. The polarisation of this band immediately gives the symmetry of the electronically excited state. This band will be referred to as the A_0^0 band, following Brand's nomenclature. On either side of it are the bands K_0^0 and L_0^0, which can be assigned to (1—0) and (0—1) transitions, involving excitation of one quantum of the out-of-plane hydrogen bending vibration of symmetry B_g. The analysis requires the A_0^0 band to be a perpendicular type C band and the two forbidden bands K_0^0 and L_0^0 to be mainly parallel type A bands with a small perpendicular component.

Some of the absorption bands of both glyoxal and dideuteroglyoxal, in particular the A_0^0 bands, have been investigated here under high resolving power, in order to determine their polarisation directly from their rotational structures and also, by analysis of these, to determine the dimensions of the molecule in the ground and the excited state. The bands have a complex rotational structure; it must be emphasised that the analysis offered here is one that is consistent with their appearance under the resolution that has been achieved.

Experimental

Dideuteroglyoxal was prepared by Riley and Friend's method [8] from tetradeuteroethylene, made from pure samples of 1 : 2-dibromodeuteroethylene prepared by Wilson and Wylie.[9] 3 c.c. of dry and freshly purified dioxan were moistened with 1 drop of 99·6% deuterium oxide and added to approximately 2 g. of dry " AnalaR " 16—24 mesh zinc dust. 3 c.c. of dibromodeuteroethylene were added and the reactants slowly heated in a glycerol bath. A slow current of dry nitrogen at atmospheric pressure swept the generated deuteroethylene through a trap at −78° into a trap cooled by liquid nitrogen, where it condensed. After 2 hr. this trap was isolated and evacuated, and its contents allowed to evaporate into an evacuated 8 l. glass storage reservoir. The deuteroethylene was purified by passing it repeatedly at low pressure through a trap at −78°.

Dideuteroglyoxal was prepared by distilling the deuteroethylene several times *in vacuo* through a hard-glass tube packed loosely with selenium dioxide and powdered phosphoric oxide (1 : 1 w/w). Initially this tube was heated electrically to about 200°. This temperature was not exceeded during reaction, otherwise excessive charring occurred. After several vacuum resublimations to remove traces of selenium and phosphoric oxide, the product was distilled into a trap at −78° sealed to a fused silica absorption cell 50 cm. long.

The apparatus (all glass) was baked out under vacuum beforehand. Reactants were added in a countercurrent of dry nitrogen.

Glyoxal was made directly from cylinder ethylene by the same method. In each case, the product was stable indefinitely when stored under vacuum at −78°.

In the dideuteroglyoxal spectrum there were no discrete bands which could be assigned to either the monodeutero- or dihydrogen-glyoxal, different samples possessing identical absorption.

[7] Ingold and King, *J.*, 1953, 2708.
[8] Riley and Friend, *J.*, 1932, 2342.
[9] Wilson and Wylie, *J.*, 1941, 596.

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However, owing to the extended and complex structure of the bands, they may have contained weak unrecognised lines due to hydrogenic impurities.

Absorption spectra were photographed in the first order of a 20 ft. Ebert grating spectrograph [10] with, as light source, a high-pressure xenon arc with a 2 mm. thickness of Chance Bros. glass type OY10 as a filter. Spectra were recorded on Kodak L.15 plates; iron-arc comparison spectra were superposed immediately before or after each exposure. The glyoxal was kept at some fixed temperature between $-20°$ and $-30°$ during exposures. The cell itself was at 20°; some spectra were also recorded with the cell cooled to $-20°$ by external circulation of cold alcohol, but no measurable variation in intensity distribution was observed. The cell could not be heated above room temperature, owing to the rapid polymerisation of the glyoxal which occurred.

The plate dispersion in the absorption region was approximately 0·65 Å/mm. and the resolving power was 150,000. This corresponded to a minimum separation between resolvable lines of approximately 0·04 mm. Lines were measured from the plate in both directions, a travelling microscope reading to 0·01 mm. being used, and mean values taken. The wavelengths of iron-arc reference lines were fitted to a calculated dispersion curve for the spectrograph,[11] which was then used to calculate absorption line wavelengths. These were then converted into vacuum wave numbers.

Discussion

Rotational Energy Levels.—The planar glyoxal molecule is a near-prolate asymmetric top, with moments of inertia $I_a \ll I_b < I_c$. The asymmetry parameter $\kappa = (2B - A - C)/(A - C) \simeq -0{\cdot}99$ in the ground state, A, B, and C being corresponding rotational constants.

There is probably no gross change of shape of the molecule upon electronic excitation. Otherwise, by the Franck–Condon principle, long progressions in that excited-state vibration which tends to bring this state into the shape of the ground state should be observed, as in acetylene.[7] If the excited state were non-planar, then its energy levels would "split" into two components, leading to an apparent doubling of spectral lines; if this splitting were large, two sets of vibrational levels, with different vibronic (vibrational–electronic) origins, would appear; if it were small, the doubling would appear in the rotational structure. Neither effect was observed. Brand's vibrational analysis, and our rotational analysis, are both consistent with a planar excited state. Of the four possible electronic symmetry states of an excited state of C_{2h} symmetry, transitions to two of them, of symmetries A_u and B_u, are allowed. The former transition is polarised along the c-axis, the latter in the (a, b) plane.

The energy levels of a prolate symmetric top ($I_b = I_c$, $\kappa = -1$) are given by

$$E(J, K) = BJ(J + 1) + (A - B)K^2 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where J and K are quantum numbers associated with the total angular momentum and its component along the a-axis respectively, with $J \geqslant K$.

A slightly asymmetric top has similar energy levels, but all levels with $K > 0$ are "split" into two components, the splitting being greatest for levels of low K-value. When the splitting is negligibly small, a good approximation to the energy levels is given by

$$E(J, K) = DJ(J + 1) + (A - D)K^2 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $D = \frac{1}{2}(B + C)$.

The energies of levels of low K can only be obtained by a perturbation treatment or by other approximate methods. Here, a Mathieu function approximation was used. This method is based on the similarity between the matrix equations which give characteristic

[10] King, *J. Sci. Instr.*, in the press.
[11] Callomon, *Canad. J. Phys.*, 1956, **34**, 1046.

values for Mathieu's differential equation and those giving the energy levels of an asymmetric rotor.[12] There exist comprehensive tables of these characteristic values.[13] In order to compare observed and calculated rotational structure, it was not necessary to calculate energy levels to the degree of accuracy envisaged by Golden;[12] his first- and second-order correction terms were ignored, and his expression for the energy levels approximated still further by the equation;

$$E(J, K) = CJ(J + 1) + (A - D)b_K(\mathrm{s}) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $b_K(\mathrm{s})$ is the characteristic value giving rise to the requisite odd or even solution of Mathieu's equation, with

$$\mathrm{s} = (B - C)/(A - D)[J(J + 1) - \{1 + 1/2J(J + 1)\}] \quad . \quad . \quad . \quad (4)$$

By use of these equations large numbers of energy levels could be calculated rapidly to a suitable degree of accuracy.

Rotational Structure of Bands.—When the symmetric-top approximation to the energy levels is valid for both combining states, selection rules predict that each $(K' - K'')$ transition * should consist of a P, Q, and R branch, due to the accompanying changes in quantum number J (except in the $K'' = 0$, $\Delta K = 0$ transition, where the Q branch is missing). Each of these " sub-bands " can be referred to an origin, which is where the hypothetical $J'' = 0$, $\Delta J = 0$ Q-line would occur. The frequencies of these sub-band origins are given by the equations:

$$\nu_0 = \nu_{00} + \{(A' - D') - (A'' - D'')\}K^2 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

for parallel-type bands with $\Delta K = 0$, and

$$\nu_0 = \nu_{00} + (A' - D') \pm 2(A' - D')K + [(A' - D') - (A'' - D'')]K^2 \, . \quad (6)$$

for perpendicular-type bands with $\Delta K = \pm 1$ respectively, ν_{00} being the vibrational origin of the band. The restriction $J \geqslant K$ on the energy levels causes certain lines to be missing in each sub-band; for example, in a perpendicular-type transition, the line R(K) is the R line nearest to the origin of the Kth sub-band.

For transitions between levels of low K number in a slightly asymmetric top, such patterns as are given by the above equations will disappear, owing to the splitting and displacement of the energy levels from their equivalent symmetric-top values.

The line intensities within a band are obtainable from the tables given by King, Hainer, and Cross.[14] These values must be combined with appropriate Boltzmann factors for the population of the ground-state levels involved, and also with statistical weight factors for the nuclear spins of the atoms in the molecule, as in acetylene.[7]

Observed Structure of the A_0^0 *Bands.*

Plate 1 shows the rotational structure of the A_0^0 band of glyoxal near the band origin. A central intensity minimum † occurs. To the short wavelength side of this, a series of heads labelled $K_2, K_3, \cdots$ each degraded towards the red, extend with increasing separation. A considerable amount of fine structure can be observed between these heads: similarly

* When describing transitions by pairs of symbols in parentheses, the upper state is placed first; primes and seconds refer to the upper and the lower state respectively.

† Absorption lines are shown black. " Intensity " refers to intensity of absorption.

[12] Golden, *J. Chem. Phys.*, 1948, **16**, 78.

[13] National Bureau of Standards, " Tables Relating to Mathieu Functions," Columbia Univ. Press, 1951.

[14] Cross, Hainer, and King, *J. Chem. Phys.*, 1944, **12**, 210.

spaced structure, of higher intensity of absorption, is also found on the long-wavelength side of the intensity minimum.

Plate 2 is a similar reproduction of the A_0^0 band of dideuteroglyoxal. Again, heads degraded towards the red extend in regular sequence towards short wavelengths. In both spectra these heads extend a considerable distance beyond the region shown; their frequencies are listed in Table 1. At wavelengths longer than those shown, both spectra consist of complex mazes of overlapping lines, which contain no prominent features and could not be analysed.

TABLE 1. *Frequencies (cm.$^{-1}$) and assignments of sub-band heads in the A_0^0 bands of glyoxal and dideuteroglyoxal.*

Glyoxal	Dideuteroglyoxal	K''	Glyoxal	Dideuteroglyoxal	K''
21,996·85	22,029·68	4	22,041·53	22,057·08	12
22,001·66	32·62	5	48·10	61·08	13
6·66	35·74	6		65·20	14
11·89	39·00	7		69·47	15
17·08	42·36	8		73·82	16
23·06	45·86	9		78·34	17
28·96	49·45	10		83·02	18
35·12	53·21	11			

The frequencies of the two sets of heads in Table 1 could be fitted to eqn. (6) with $\Delta K = +1$. In a perpendicular transition, these heads could be either the unresolved Q-branches of low J'' numbering, or else R-heads of the sub-bands. They were taken to be the latter, for the following reasons. First, the intensities of the observed heads remain considerable up to high values of K''; whereas the theoretical intensities of Q-branches drop rapidly as K'' increases. Secondly, the heads remain sharp at high K'' values, whereas missing lines would be expected to give unresolved Q-maxima rounded edges in these circumstances. Thirdly, Q-maxima would be expected to persist with considerable intensity, and with small deviation from their positions as calculated from eqn. (6), back to the band origin ν_{00}; whereas in both spectra, the positions of intensity maxima become very irregular at wavelengths longer than those of the points labelled $K'' = 4$. As will be shown below, comparison of calculated and observed positions of the heads justifies their assignment as R-heads.

The next problem was to assign the correct K'' numbering to these heads, since the values of the rotational constants in eqn. (6) depend on this assignment. On fitting the head frequencies in Table 1 to a quadratic equation by a least-squares approximation [15] and evaluating from this the constants in eqn. (6), we found three sets of rotational constants for each molecule which lay within the error limits permitted by the electron-diffraction ground-state dimensions and their associated errors. These are shown in Table 2, and correspond to the three possible numberings of the sub-band heads labelled α, β and γ. The α-numbering is shown beside the frequencies listed in Table 1. Furthermore, it was not possible to associate, say, the α-numbering for glyoxal with the β-numbering for dideuteroglyoxal, since such combinations were found to correspond to highly improbable sets of molecular dimensions.

The quadratic equations for the band heads for each molecule predict that the heads themselves will converge to a head. This " head of heads" can be clearly seen for dideuteroglyoxal in Plate 2. It cannot be distinguished in the glyoxal spectrum; calculation shows that here there are fewer sub-band heads to absorb light at the actual convergence limit frequency than there are in the case of dideuteroglyoxal.

Theory predicts that in sub-bands of high K'' numbering in a perpendicular transition, only the R branches have appreciable intensity. It is possible to pick out series of lines assignable as R branches in several of the sub-bands of the glyoxal spectrum. In Plate

[15] Birge, *Rev. Modern. Phys.*, 1947, **19**, 298.

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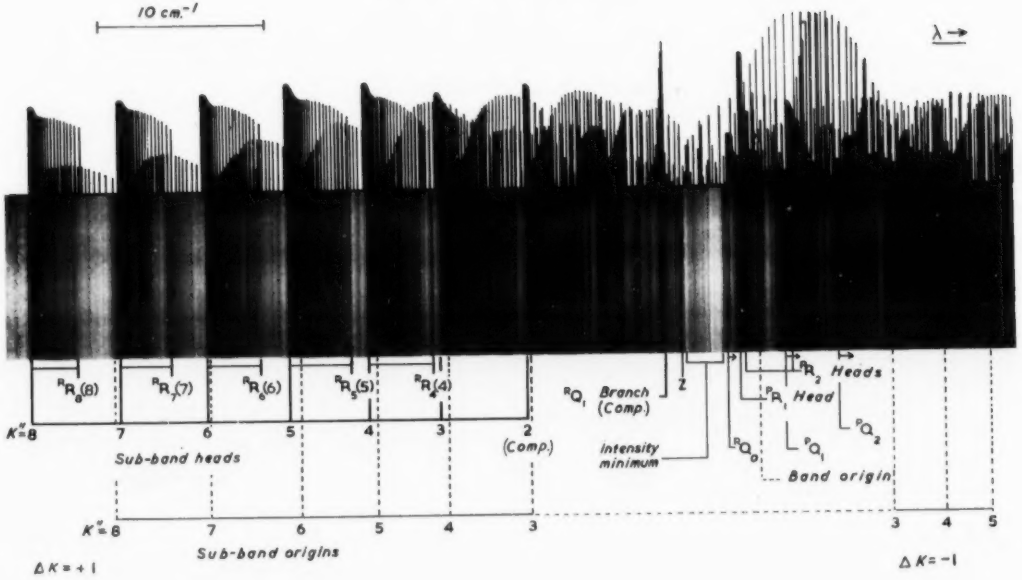
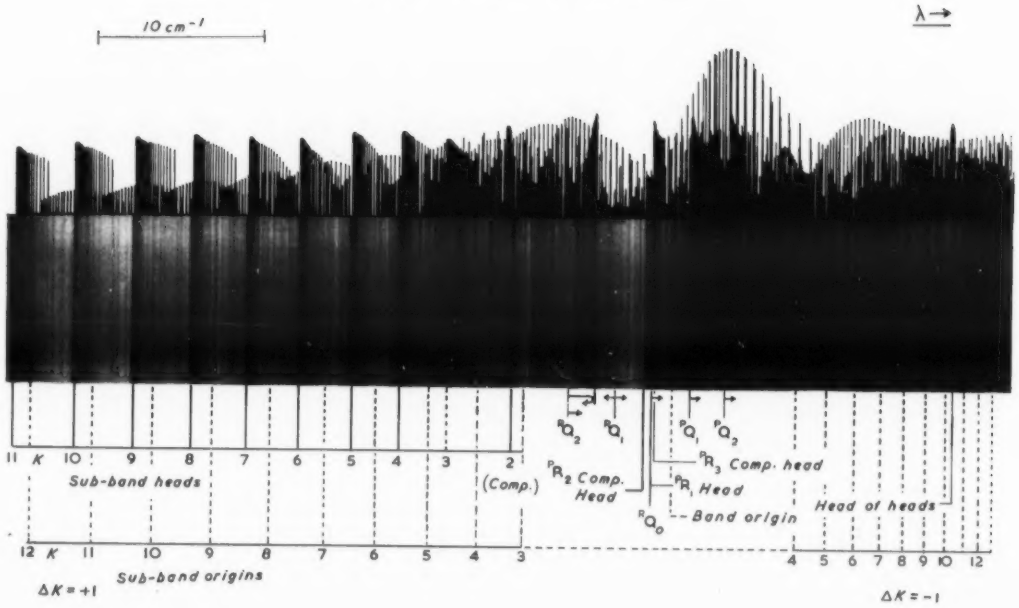
PLATE I. A_0^0 *band of glyoxal.*



[*To face p. 5058*]

PLATE 2. A_0^v *band of dideuteroglyoxal.*



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1 these are seen as groups of fairly intense lines to the long-wavelength side of the heads labelled $K_4, K_5, \cdots$. Such series were not defined clearly in the dideuteroglyoxal spectrum, since it is overlapped in the appropriate spectral region by the rotational structure of another band with its origin at approximately 22,116 cm.$^{-1}$. The frequencies of groups of resolved R lines in the glyoxal spectrum are given in Table 3. The lines listed were only just resolvable and could not be measured with extreme accuracy; however, some information could be gleaned from them. Other groups of R lines associated with sub-band heads of higher K'' numbering could be distinguished on the plates, but were not clearly resolvable.

TABLE 2. *Rotational constants (cm.$^{-1}$) obtained by least-squares approximation of heads in Table 1 to equation* (6).

$(CHO)_2$				$(CDO)_2$			
Head Numbering	$(A''-D'')$	$(A'-D')$	S.D.	Head Numbering	$(A''-D'')$	$(A'-D')$	S.D.
(α) $K''=4$—13	1·7657	1·8795	±0·0073	(α) $K''=4$—18	1·1396	1·2033	±0·0045
(β) $K''=5$—14	1·6518	1·7657	±0·0081	(β) $K''=5$—19	1·0758	1·1396	±0·0049
(γ) $K''=3$—12	1·8796	1·9934	±0·0065	(γ) $K''=3$—17	1·2033	1·2671	±0·0041

Also, for $(CHO)_2$, $(A'-D')-(A''-D'')=0{\cdot}11387\pm0{\cdot}00061$ cm.$^{-1}$; for $(CDO)_2$, $=0{\cdot}06375\pm0{\cdot}00028$.

The J numbering of the R lines in each sub-band depends on the K numbering of the sub-band head; that is, on which of the assignments α, β, or γ in Table 2 is taken as correct. However even with this ambiguity, it was possible to calculate from the figures in Table 3 that the origin of each sub-band lay some 5 cm.$^{-1}$ to the red of the corresponding sub-band head. This implied that the Q-branch of the K''th sub-band was buried beneath the R-head of the (K''-1)th sub-band; and it can be seen from Plate 1 that the R-heads possess a diffuse and extended intensity at low K'' values, where the intensity of the underlying Q-branch would be expected to be appreciable.

TABLE 3. *Frequencies of* R*-lines in glyoxal sub-bands.*

$J''=$ / K''	4	5	6	7	8	9	10	11	12	13	14	15
4	21,993·01	93·35	93·62	93·84	94·16							
5		21,998·00	98·33	98·63	98·82	99·06						
6			22·003·35	03·60	03·83	04·08	04·26	04·46	04·66	04·86	05·02	05·23
7				22,008·79	09·06	09·27	09·48	09·69	09·87	10·10	10·30	

Some preliminary calculations were then carried out. Planar molecular models were assumed for the ground and excited states, with dimensions that yielded rotational constants approximately corresponding to the values for the α, β, and γ assignments of Table 2, and which yielded values of D_H'' and D_H' appropriate to a sub-band head-origin separation of approximately 5 cm.$^{-1}$ and a spacing between R-lines approximating to that observed. Using these models, we calculated the frequencies and positions of all lines near the band origin for a type-C transition for both glyoxal and dideuteroglyoxal; the Mathieu function approximation was used to obtain the energy levels.

In all the calculated glyoxal spectra, the stronger lines formed a clear overall pattern of intensity, which showed that the band origin ν_{00} lay some 3—4 cm.$^{-1}$ to the red of the central intensity minimum. This overall pattern was very similar in all three sets of calculated spectra, a fact which enabled the K-numbering of the sub-bands to be fixed definitely but, conversely, made it difficult to use the observed pattern of lines to obtain accurate values of the rotational constants.

The approximate position of the band origin, and the approximate head-origin separation in the sub-bands being known, the α-numbering of the sub-band heads in Table 2 can be

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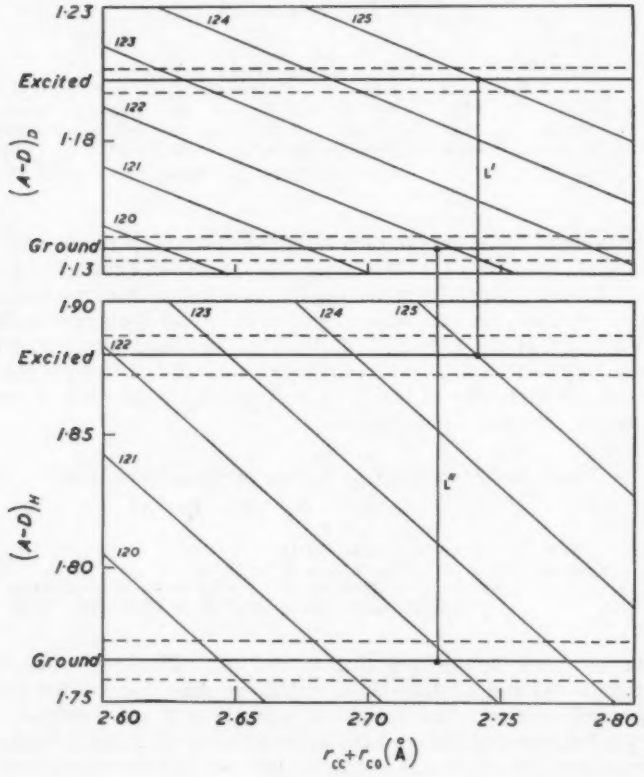
assigned as correct. This immediately gives the J numbering of the R lines in the sub-bands.

For the symmetric-top approximation, the separation of the line R(J) from the corresponding sub-band head is given by the equation:

$$\Delta\nu_J = (\Delta\nu_H - 2D') - (3D' - D'')J - (D' - D'')J^2 \quad . \quad . \quad . \quad (7)$$

where $\Delta\nu_H$ is the head-origin separation in the sub-band. The accurate positions of the sub-band heads were calculated by using the α-numbering in Table 2, and the separations of the R lines in Table 3 from the corresponding heads in each sub-band were fitted to

FIG. 1. *Nomograph for calculation of dimensions of glyoxal. The sloping lines correspond to different values of ∠CCO. The broken lines show the limits of error of the observed values of (A − D).*



eqn. (7) by least-squares approximation. This gave a value of D_H'' and D_H' for each sub-band considered. These were combined to give mean values for the two constants, giving each individual value a weighting inversely proportional to the sum of the squared residuals in the corresponding calculation. This gave:

$$D_H' = 0{\cdot}1479 \pm 0{\cdot}0095 \qquad D_H'' = 0{\cdot}1520 \pm 0{\cdot}0095 \text{ cm.}^{-1}$$
$$(D_H' - D_H'') = -0{\cdot}00413 \pm 0{\cdot}00070 \text{ cm.}^{-1}$$

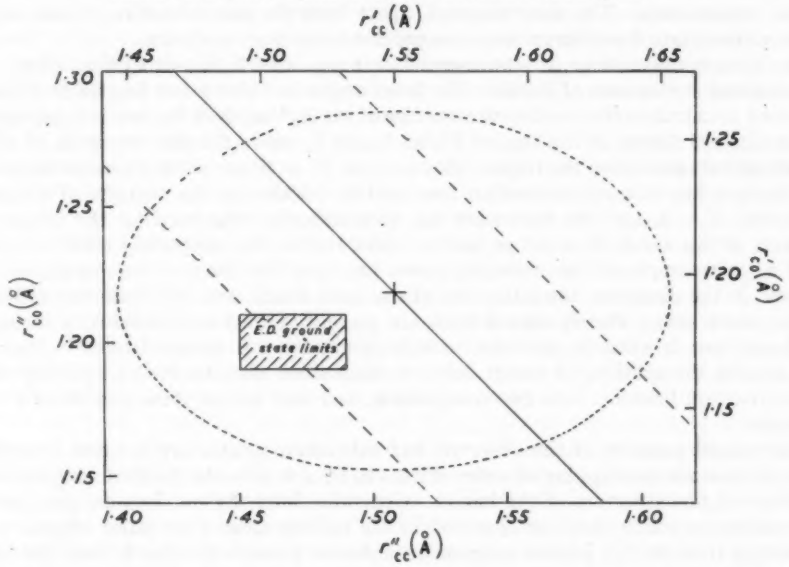
The Calculation of Molecular Dimensions.—If values are assumed for the C–H bond length and angle, the other molecular parameters r_{CC}, r_{CH}, and ∠CCO can now be calculated for each state of the molecule. It is also necessary to assume that, for the planar

molecule in its lowest vibrational state, $I_c = I_a + I_b$; that is, the inertial defect is set equal to zero.

Various molecular models were assumed, and their rotational constants calculated by Hirschfelder's method.[16] The derivatives of $(A - D)_H$, $(A - D)_D$, and D_H were determined with respect to each of the three parameters r_{CO}, r_{CH}, and ∠CCO. These derivatives could be taken as constant over the range of dimensions which it was necessary to consider.

It was found that $d(A - D)_H/dr_{CO}$ and $d(A - D)_H/dr_{CO}$ were almost equal in sign and magnitude; this was also true in the case of dideuteroglyoxal. Hence calculated values of $(A - D)_H$ and $(A - D)_D$ were each plotted as a function of $(r_{CO} + r_{CO})$, giving series

FIG. 2. *The errors associated with the determined bond lengths.*



of straight lines corresponding to different values of ∠CCO, as shown in Fig. 1. There existed, for each electronic state, one value of $r_{CO} + r_{CO}$ (the lines L′ and L″) and of the angle which corresponded to the observed values of $(A - D)_H$ and $(A - D)_D$ (Table 4).

TABLE 4. *Parameters of the ground and the excited state.*

	$r_{CO} + r_{CO}$	∠CCO
Ground	2·726 ± 0·062 Å	121·9 ± 1·3°
Excited	2·742 ± 0·062 Å	125·0 ± 1·3°

The quoted deviations are determined from Fig. 1.

TABLE 5. *Bond lengths (very approximate) in the ground and the excited state.*

	r_{CC}	r_{CO}
Ground	1·50 Å	1·22 Å
Excited	1·55 Å	1·19 Å

Since the derivatives dD_H/dr_{CC} and dD_H/dr_{CO} differ considerably in magnitude, it was now possible to obtain individual values for the C–C and C–O bond lengths in each electronic state (Table 5), the observed D_H values being used together with the figures in Table 4. *It*

[16] Hirschfelder, *J. Chem. Phys.*, 1940, **8**, 431.

is important that these individual bond lengths should not be regarded as being particularly accurate. Their individual standard deviations are of the order of 0·1 Å, and have little meaning. The permitted values for the individual bond lengths, however, are always correlated, in a sense, by the permitted values for their sums in Table 4.*

The deviations involved are shown in Fig. 2. The shaded rectangle shows the limits of error of bond lengths from the electron diffraction measurements. The straight line shows the most probable value of $r_{CO} + r_{CO}$; the broken lines flanking it show the corresponding standard deviations. The area contained within the ellipse gives the uncorrelated individual values of r_{CO} and r_{CO} that are possible. The ellipse is centred here on the most probable values for the bond lengths given in Table 5. In the ground state, the possible electron-diffraction values lie within the ellipse, and also lie largely within the area bounded by the broken lines. The same diagram, apart from the shaded rectangle, also applies to the excited state if a different set of co-ordinates are used, as shown.

In all these calculations, it was assumed that $r_{CH} = 1{\cdot}071$ Å and $\angle CCO = 120°$.

Calculated Appearance of Bands.—The bond angles in Table 4 and lengths in Table 5 † were used to calculate the theoretical structure of the A_0^0 bands of the two isotopic species. The results are shown at the tops of Plates 1 and 2, where the line strengths of all the individual lines present in the regions shown up to $J'' = 40$ are plotted against frequency. The Mathieu-function approximation was used in calculating the energies of rotational levels with $K < 4$, and the symmetric-top approximation was used for the others. In diagrams of this nature it is not possible to show readily the integrating effect which the use of a spectrograph of finite resolving power has upon the observed lines in a spectrum; however, in the diagrams, the intensities of sub-band heads, and of Q-branches at low J'' values, where many closely-spaced lines are present, have been deliberately increased. The bands are labelled in accordance with symmetric-top nomenclature.[17] Near the band origins, the splitting of energy levels in each state often leads to a splitting of the (symmetric-top) branches into two components, and only one of these may form a head, as shown.

The overall patterns of the observed and calculated spectra are in good agreement. There is too much overlapping of series of lines to be able to make detailed assignments of the observed fine structure of the bands. Generally, intensity maxima are predicted at the positions in which they are observed in the regions around the band origins. It is noteworthy that the ${}^RQ_1$ branch component is shaded towards the blue in both the calculated and the observed glyoxal spectrum, and that one ${}^RQ_2$ branch component forms a head shaded towards the blue in the dideuteroglyoxal spectrum, as indicated by the curved arrow. There is one apparent minor head, marked Z, in the glyoxal spectrum, which cannot be accounted for; it may be due to some weak $\Delta K = 2$ transition, or else to a P-branch forming a head at a high J'' numbering.

Rotational Structure of Other Bands.—If two transitions have a vibronic state in common, then rotational analysis should yield a common $(A - D)$ value for this state. It is theoretically possible to use this fact to deduce the correct K'' numbering of sub-bands. This was not practicable here, since the deviations in the first-order terms in the quadratics for the sub-band heads were too large in comparison with the second-order terms. Many vibrational bands were overlapped by other bands, so that only a few sub-band heads could be measured, giving correspondingly large deviations for the rotational constants. The C_0^0 band, at 22,487 cm.$^{-1}$, was fairly well defined; by Brand's analysis, this is a perpendicular band with the same ground state as the A_0^0 band. One K numbering of

* If it is assumed that the quoted electron-diffraction C–C and C–O bond lengths are correct, then the following set of approximate excited state dimensions can be deduced: $r'_{CO} = 1{\cdot}56$ Å, $r'_{CO} = 1{\cdot}14$ Å, $\angle CCO = 126{\cdot}3°$.

† The values used have been rounded off to 2 decimal places in Table 5.

[17] Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, 1945, p. 426.

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the C_0^0 sub-band heads gave: $(A'' - D'')_H = 1{\cdot}793 \pm 0{\cdot}025$ cm.$^{-1}$; $(A' - D')_H = 1{\cdot}911 \pm 0{\cdot}025$ cm.$^{-1}$; $(A' - D')_H - (A'' - D'')_H = 0{\cdot}1184 \pm 0{\cdot}0029$ cm.$^{-1}$. The value for $(A'' - D'')$ can be compared with that for the A_0^0 band.

Under high resolution, the K_0^0, K_1^0, and K_2^0 bands are clearly parallel-type bands, as required by the vibrational analysis. Each has a weak perpendicular component. The parallel component in each consists of a series of heads, each shaded toward the red, extending towards the blue from a strong intensity maximum. These heads could be fitted to eqn. (5) to give reasonable values of the rotational constant function therein; for example, the K_0^0 bands in each spectrum gave $(A' - D')_H - (A'' - D'')_H = 0{\cdot}109$ cm.$^{-1}$ and $(A' - D')_D - (A'' - D'')_D = 0{\cdot}062$ cm.$^{-1}$. However the complete analysis of these bands is another problem.

Conclusion.—The observed structure of the A_0^0 bands of both isotopic species is consistent with a planar, centrosymmetric *trans*-configuration in both the ground and the excited state, with a perpendicular type C transition between them. The main postulates upon which Brand based his vibrational analysis are confirmed, and hence if the A_0^0 band is the (0–0) band, the excited state has A_u electronic symmetry.

Fairly accurate values for the ∠CCO and the sum of the C–C and C–O bond lengths can be obtained from the analysis of the rotational structure; but there is considerable uncertainty in the individual values to be assigned to the bond lengths in the ground and the excited state. This is partially due to the fact that analysis of the rotational structure of bands yields information about the three principal moments of inertia of the molecule, and the geometry of the glyoxal molecule is such that substitution of the hydrogen atoms by deuterium does not greatly alter the momental parameters. However, the ground-state dimensions that have been derived are in approximate agreement with those obtained by electron diffraction. In the excited state, the ∠CCO increases by some 3°, compared with the ground state, and the indications are that the C–C bond may increase slightly in length, and the C–O bond decrease by a smaller amount.

The electronic transition investigated in this paper is very weak ($f \sim 0{\cdot}00004$ in solution) [18] and is ascribed to the promotion of one of the non-bonding oxygen electrons, which in the ground state fill two almost degenerate molecular orbitals, into a π-type orbital. There are two such configurations of A_u electronic symmetry; in one of them, the promoted electron is in a π-orbital that is essentially bonding between the carbon atoms and antibonding between the carbon and oxygen atoms; the other is antibonding with respect to both the C–C and C–O bonds. In neither state would it be expected that the C–O bond decreases in length relative to the ground state, if this in fact occurs. Neither does such a decrease agree with Brand's assignment of the (mainly) C–O stretching frequency of symmetry A_g dropping from approximately 1740 to 1390 cm.$^{-1}$ upon electronic excitation.

However, simple molecular-orbital pictures may not be appropriate here.[19] Thus they ignore the charge redistribution which takes place, electronic charge being transferred from the oxygen atoms towards the centre of the molecule in the course of the transition. This, also, must affect the bond lengths, and might tend to shorten the C–O bonds and increase the C–C bond in the excited state.

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William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, July 24th*, 1957.]

[18] McMurry, *J. Chem. Phys.*, 1941, **9**, 241.
[19] Orgel, *J.*, 1955, 121.

1011. *The Conductance of Solutions in which the Solvent Molecule is "Large." Part III.* Amine Picrates in Tritolyl and Tri-(2-ethylhexyl) ("Trioctyl") Phosphates.*

By C. M. French and D. F. Muggleton.

The conductances of five amine picrates in two phosphoric esters have been examined at 40° in the range $2{\cdot}6 \times 10^{-6}$—$8{\cdot}55 \times 10^{-4}$N. In addition, one of these systems was investigated at 25° and 55°. The conductance of tribenzyl- and triphenyl-ammonium picrates appears to be controlled principally by a molecular dissociation in addition to a limited ionisation. The conductance relationships of the tetraethyl-, tetra-*n*-butyl-, and tetra-*n*-pentyl-ammonium picrates show specific solvent effects. Among the anomalies are an unexpectedly high ion-pair dissociation constant K in tritolyl phosphate; a decrease in K with rise of temperature in trioctyl phosphate; a high ratio for both the dissociation constant and limiting equivalent conductance of tetra-*n*-butyl- to tetraethyl-ammonium picrates; a very low Walden product in trioctyl phosphate, and the appearance of a maximum in the variation of the Walden product with temperature.

For conductivity relationships in solutions where the solvent molecule is large it may no longer be possible to maintain that the solvent is an isotropic continuum. Elliott and Fuoss [1] suggested that in such systems the most obvious correction is to allow for the probability that a small ion can pass through certain configurations of large solvent molecules without displacing them. The ion, then subject to much smaller retarding forces than those computed from the observed viscosity, would show a relatively high ionic mobility. The electrical properties of such a discontinuous solvent would probably differ appreciably from those of the idealised medium, and the rôle of the observed, macroscopic dielectric constant may be difficult to assess.

Conductance measurements in such solutions should furnish information on the principles involved in the dynamics of electrolytic conductance not available from similar work with other systems. However, such solvents already examined are restricted to tritolyl phosphate,[1] 2-hydroxyethylamine,[2] 2 : 2′ : 2″-trihydroxytriethylamine, and *N*-ethyl-*N*-2-hydroxyethylaniline,[3] 2 : 2′-dihydroxydiethylamine,[4] and a series of dialkyl phthalates.[5,6] We examined the conductance of more salts in tritolyl phosphate, and extended the range of solvents to tri-(2-ethylhexyl) phosphate and triethyl phosphate (the results for the latter appear anomalous in several respects, and are not presented here).

Elliott and Fuoss [1] and others [7,8] reported that certain amine picrates dissociated both molecularly and ionically in some solvents. Measurements were therefore made with tribenzylammonium and aniline picrates as solutes, in addition to tetraethyl-, tetra-*n*-butyl-, and tetra-*n*-pentyl-ammonium picrates which were used to examine the effect of ion size.

Experimental

Measurements were made and solutes prepared and purified as before.[9] The two solvents were purified as follows: commercial tritolyl phosphate, a mixture of ten isomers with the

* Part II, *J.*, 1957, 2131.

[1] Elliott and Fuoss, *J. Amer. Chem. Soc.*, 1939, **61**, 294.
[2] Briscoe and Dirkse, *J. Phys. Chem.*, 1940, **44**, 388.
[3] Bhattacharyya and Nakhate, *J. Indian Chem. Soc.*, 1947, **24**, 1, 99.
[4] Bhattacharyya and Bhadra, *Current Sci.*, 1947, **16**, 117.
[5] French and Singer, *J.*, 1956, 1424.
[6] *Idem, ibid.*, p. 2428.
[7] Witschonke and Kraus, *J. Amer. Chem. Soc.*, 1947, **69**, 2472.
[8] Fuoss, Edelson, and Spinrad, *ibid.*, 1950, **72**, 327.
[9] French and Muggleton, *J.*, 1957, 2131.

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TABLE 1. *Equivalent conductivity* (X = *picric acid residue*).

Solute	25° 10^4c	25° $10^3\Delta$	40° 10^4c	40° $10^3\Delta$	55° 10^4c	55° $10^3\Delta$
			(a) *Tritolyl phosphate*			
Et_4NX	30·751	7·806	37·552	22·51	32·370	45·16
	27·393	8·063	30·173	23·77	26·176	48·13
	19·716	8·741	26·214	24·13	20·509	51·32
	13·651	9·756	17·993	27·06	13·847	57·56
	10·090	10·94	15·293	28·82	9·9723	62·94
	6·8807	12·51	10·973	32·11	6·0732	71·99
	5·4684	13·26	7·4824	36·64	5·0436	76·81
	3·7707	15·00	5·8592	39·62	4·4129	77·91
	1·6789	18·59	3·6615	46·89	2·5006	88·27
	1·4948	19·26	2·0527	55·50	1·1054	101·0
	0·64860	22·51	1·2484	62·14	0·87997	105·1
	0·49608	23·61	0·92010	68·65		
	0·11370	27·36	0·40103	75·74		
			0·15544	84·73		
			(b) *Trioctyl phosphate*			
Et_4NX	6·4148	4·602	5·5970	7·954	5·6093	13·47
	5·1534	4·900	2·9879	11·24	3·6164	15·91
	3·0812	5·963	2·6964	11·87	3·3442	16·26
	2·5793	6·470	1·1835	18·07	2·0999	19·50
	1·5161	8·198	0·66578	22·01	1·5252	22·89
	0·84168	10·66	0·44652	24·84	0·83198	29·97
	0·58349	12·25	0·23149	32·12	0·70252	32·11
	0·52914	12·92	0·12826	41·25	0·56427	34·55
	0·25031	16·81	0·10130	44·76	0·34781	42·49
	0·21448	18·13			0·20759	51·90
	0·11478	21·94			0·16225	57·70
					0·08377	71·62
					0·042304	93·44
					0·025998	103·52

Solute	*Tritolyl phosphate at* 40° 10^4c	$10^3\Delta$	10^4c	$10^3\Delta$	*Trioctyl phosphate at* 40° 10^4c	$10^3\Delta$	10^4c	$10^3\Delta$
Bu_4NX	85·549	16·30	9·3248	27·08	43·341	5·812	1·4766	18·46
	80·593	16·49	7·2498	29·30	22·765	6·520	0·85224	23·23
	49·434	17·78	5·6093	31·31	18·741	6·842	0·51017	28·74
	38·703	18·50	2·9587	35·72	13·584	7·587	0·26308	40·15
	28·046	20·00	2·0355	37·88	6·2888	10·14	0·11166	52·32
	24·196	20·70	1·7642	39·09	3·3790	13·21		
	18·675	22·49	1·2916	40·49				
	12·857	24·78	0·21523	46·42				
$(C_5H_{11})_4NX$	59·761	16·49	7·6663	28·38	46·909	5·125	2·6137	13·67
	41·202	17·78	5·8725	30·44	33·699	5·473	1·3140	18·69
	33·653	18·85	5·4790	31·40	24·259	5·938	0·70565	24·49
	31·746	19·12	4·0743	32·67	14·223	7·020	0·43985	30·35
	23·758	20·68	2·3991	36·00	6·7702	9·002	0·21176	43·06
	18·908	22·07	1·1855	39·59	4·4568	10·72	0·12147	52·44
	14·326	23·71	0·65966	42·01				
	9·4396	26·68	0·15338	45·81				
$(Ph\cdot CH_2)_2NHX$	32·503	7·792	3·8124	12·86	17·862	3·215	0·59342	4·896
	28·386	8·097	1·2601	15·19	13·487	3·442	0·28078	6·442
	22·794	8·433	0·59406	17·56	6·1057	3·941	0·16491	8·616
	13·997	9·741	0·39791	17·94	5·1082	4·004	0·14057	9·741
	8·8215	10·82	0·20751	22·44	1·9653	4·313	0·079347	12·67
	6·7745	11·57			0·98992	4·592		
$Ph\cdot NH_3X$	59·671	1·635	5·3712	3·312	76·573	0·6567	4·3735	1·862
	44·053	1·787	5·1220	3·349	51·854	0·7624	2·6534	2·232
	34·344	1·920	3·8825	3·611	29·486	0·8816	1·9187	2·500
	26·474	2·084	2·0274	4·419	23·520	0·9610	1·3883	2·746
	19·211	2·284	1·9751	4·320	13·991	1·219	0·64398	3·555
	13·912	2·528	0·70683	5·481	10·724	1·329	0·43696	4·061
	7·9596	2·975			6·1661	1·631	0·22102	4·876

purely *ortho*-form predominating, was kept for some weeks over dried calcium chloride, then distilled through a well-lagged column at a pressure of 4 mm., initial and final fractions (10% of the whole) being rejected. The pale yellow liquid was twice redistilled under reduced pressure, the final product being a colourless oil stable to light. The physical constants depend on the proportion of isomers present; those now recorded were sensibly constant from batch to batch and corresponded to a product consisting largely of the purely *ortho*-ester (literature values may refer to mixtures with somewhat different proportions of the isomers), b. p. 232—234°/4 mm.; n_D^{20} 1·56703; d_4^{25} 1·16484, d_4^{40} 1·15307, d_4^{55} 1·14146; dielectric constant: ε_{25} 6·73, ε_{40} 6·14, ε_{55} 5·47; viscosity (in centipoises): η_{25} 138·6, η_{40} 70·06, η_{55} 36·48; specific conductivity: κ_{25} 2·31 × 10^{-12}, κ_{40} 4·17 × 10^{-12}, κ_{55} 5·23 × 10^{-12} (lit.: b. p. 270—275°/10 mm.,[1] n_D^{20} 1·5573,[1] d_4^{25} 1·1590, d_4^{40} 1·1445, d_4^{55} 1·1304,[1] η_{20} 155·1[10]).

Tri-(2-ethylhexyl) phosphate (" trioctyl " phosphate) mixed with its own volume of ether was shaken with 5% hydrochloric acid and the organic phase filtered to remove traces of pyridine hydrochloride (pyridine was a solvent during manufacture), then shaken with sodium carbonate solution, then water, and the ether distilled off, and the ester filtered. The phosphate was then dried for 12 hr. at 100°/15 mm., and traces of solid filtered off. The now colourless ester was next intermittently shaken for 48 hr. with activated alumina (100 g./l.), stored overnight, and decanted through a fine sintered-glass disc, care being taken to exclude moisture. The phosphate was then fractionated and finally twice distilled at 3—4 mm. pressure, generous head and tail fractions being rejected (b. p. 204°/3·2 mm., 219°/5 mm.; n_D^{20} 1·44464; d_4^{25} 0·92042, d_4^{40} 0·90934, d_4^{55} 0·89766; ε_{25} 4·72, ε_{40} 4·53, ε_{55} 4·26; η_{25} 27·21, η_{40} 16·63, η_{55} 11·05; κ_{25} 4·38 × 10^{-11}, κ_{40} 9·07 × 10^{-11}, κ_{55} 13·76 × 10^{-11} (lit.: b. p. 220°/5 mm.,[2] n_D^{20} 1·443,[2] d_{20}^{20} 0·924[2]).

Results.—The variation in equivalent conductance with concentration in the ten systems is shown in Table 1.

Discussion

The conductimetric behaviour exhibits interesting features, and suggests the intervention of specific solvent effects. The chief points requiring explanation are now discussed.

The Fuoss plots for all three tetra-alkylammonium salts in both solvents were linear, and values of the limiting equivalent conductance, Λ_0, and the dissociation constant, K, obtained from them are given in Table 2. In view of the dielectric constant of both solvents (*ca.* 5), the solutes should behave as weak electrolytes, and this is confirmed for solutions in trioctyl phosphate by the values of K. In tritolyl phosphate, however, the dissociation constants are as large as in solvents of higher dielectric constant, *e.g.*, ethylene

Table 2.

Solute	Temp.	Tritolyl phosphate 10^4K	Tritolyl phosphate Λ_0	Tritolyl phosphate $\Lambda_0\eta$	Trioctyl phosphate 10^6K	Trioctyl phosphate Λ_0	Trioctyl phosphate $\Lambda_0\eta$
Et_4NX	25°	0·916	0·316	0·438	3·21	0·513	0·139
	40	0·900	0·987	0·691	0·905	1·63	0·271
	55	1·044	1·51	0·581	0·173	1·88	0·208
Bu_4NX	40	7·81	0·508	0·357	5·97	0·975	0·162
$(C_5H_{11})_4NX$	40	8·85	0·493	0·347	6·43	0·925	0·153

dichloride[11] (ε = 10·23 at 25°; $K \times 10^5$ for tetraethyl-, tetra-*n*-butyl- and tetra-*n*-pentylammonium picrates = 15·9, 22·6, and 23·8 respectively). These results are consistent with the shape of the Λ–$c^{\frac{1}{2}}$ plots which for solutions in trioctyl phosphate are typical of weak electrolytes and rise steeply at low concentrations, indicating extensive ion-pair formation. The corresponding curves for solutions in tritolyl phosphate are relatively shallow, however, and tend towards the straight-line plots obtained with strong electrolytes. Contrary to expectation the Λ–$c^{\frac{1}{2}}$ plots exhibit no minimum in the more concentrated region, although triple-ion formation might be expected at about 3 × 10^{-3}N. The absence of triple ions is confirmed by the non-linearity of the $\Lambda c^{\frac{1}{2}}$–c plots.

[10] Buttrey, " Plasticizers," Cleaver-Hulme Press, London, 1950.

The dissociation constants of these salts decrease with increase in cation size as in most solvents, but in contrast to their behaviour in acetonitrile.[9] Of particular interest too is the ratio of the dissociation constants of pairs of salts. The ratio for tetrapentyl- to tetrabutyl-ammonium picrate is similar to that in other solvents, but the ratio for tetra-*n*-butyl- to tetraethyl-ammonium picrate is very high (8·67 in tritolyl and 6·56 in trioctyl phosphate at 40°; cf. 1·42 in ethylene dichloride,[11] 1·30 in ethylidene chloride,[12] 1·16 in ethyl alcohol [13] at 25°). This suggests that specific solvent effects operate here.

The effect of temperature on the dissociation constant is not uniform, but again indicates specific solvent effects and the general complexity of factors involved. Kraus [14] pointed out that, according to Bjerrum's equation, K in solvents of low dielectric constant should increase with temperature since the dielectric constant ε changes little and εT increases. In tritolyl phosphate, however, ε decreases with rise in temperature, and there is moreover an overall decrease in εT from 25° to 55°. In trioctyl phosphate the decrease in ε with temperature rise is small and may not be significant: εT shows little change. Whereas in trioctyl phosphate there is a progressive decrease in dissociation constant with increase in temperature, consistent with the overall change in dielectric constant, but in contradiction to Kraus's suggestion, in tritolyl phosphate the dissociation constant changes little, but passes through a minimum. Perhaps in the latter solvent the opposing effects of increased kinetic energy and decreased dielectric constant with rise of temperature are nearly but not completely balanced.

The relative magnitudes of the limiting equivalent conductances of the tetra-alkylammonium picrates in the two phosphoric esters (Table 2) are similar to those of the dissociation constants. Whereas in solvents with relatively small molecules Λ_0 for the quaternary ammonium salts decreases fairly regularly with increase in cation size—an effect attributable to the increasing influence of viscosity on the larger solute ions—in both phosphates Λ_0 for tetraethylammonium picrate is very much greater than that for tetra-*n*-butylammonium picrate, the ratio for these two salts being 1·94 in tritolyl phosphate and 1·67 in trioctyl phosphate compared with approximately 1·2 in more conventional solvents. Thus the tetraethylammonium ion appears to be unexpectedly more mobile than other tetra-alkylammonium ions in these solvents.

The constancy of the Walden product may be taken as an indication of the extent to which ion size remains unchanged in different solvents. The magnitude and irregular variation in $\Lambda_0\eta$ for the tetra-alkylammonium picrates in the two phosphoric esters (Table 2) is therefore of interest. Thus in tritolyl phosphate at 40° the Walden product for tetraethylammonium picrate is more than 20% higher than its "normal" value of 0·560, and is nearly twice as great as $\Lambda_0\eta$ for the other two picrates which are correspondingly over 30% lower than "normal." In trioctyl phosphate $\Lambda_0\eta$ for tetraethylammonium picrate is again considerably greater than for the two higher homologues, but all are much less than the "normal" value. It is curious that the Walden products for tetra-*n*-butyl- and tetra-*n*-pentyl-ammonium picrates in the latter solvent are lower than $\Lambda_0\eta$ for the picrate ion in normal solvents, *e.g.*, 0·255 in ethylene dichloride [11] and ethylidene chloride,[12] 0·269 in methyl alcohol,[13] and the significance of this is not apparent. The particularly low mobilities in trioctyl phosphate might be due to extensive ion solvation in the sense of a loose association between an ion and solvent molecules. The magnitude of this effect could be different in the two phosphoric esters, tritolyl phosphate being a relatively compact molecule and trioctyl phosphate a large one with an exposed polar group at one end. It then appears that in both solvents the tetraethylammonium ion was less solvated than its two higher homologues, although this is unusual since small, highly polar ions are more likely to be highly solvated than those whose size results in

[11] Tucker and Kraus, *J. Amer. Chem. Soc.*, 1947, **69**, 454.
[12] Healey and Martell, *ibid.*, 1951, **73**, 3296.
[13] Evers and Knox, *ibid.*, p. 1739.
[14] Kraus, *J. Phys. Chem.*, 1956, **60**, 129.

considerable reduction of surface electrostatic charge density. An alternative hypothesis that the tetraethylammonium ion represents the "small" ion of Elliott and Fuoss's theory [1] does not seem tenable, particularly since at 25° $\Lambda_0\eta$ for this picrate also is less than the usual value.

The only direct comparison at present possible with conductance measurements in other systems with large solvent molecules is with Elliott and Fuoss's results [1] on tetra-*n*-butylammonium picrate in tritolyl phosphate. These are very different from ours. Elliott and Fuoss obtained a high Walden product for this solute, and found that it behaved as a weak electrolyte. The reason for these apparent discrepancies is not known, the only obvious difference between the two investigations lying in the method of purification of the solvent. The high mobility obtained for tetra-*n*-butylammonium picrate by Elliott and Fuoss, and which corresponds to that of tetraethylammonium picrate in tritolyl phosphate obtained now, was ascribed by them to a slipping of ions between solvent molecules in certain configurations, but we believe that this is too facile an explanation. The behaviour of solutes in solvents with large molecules appears complex, and may well be governed by specific solvent effects.

The effect of temperature on the Walden product is also of interest: $\Lambda_0\eta$ should vary little with temperature if ion size remains unaltered; however, for reasons suggested earlier,[5] the degree of solvation might decrease with increasing temperature, so that the mobility of the ions should increase. The Walden product increases with temperature for a series of dialkyl phthalates as solvents,[5] but in both phosphoric esters, with rise in temperature, $\Lambda_0\eta$ first increases, passes through a maximum, and finally decreases. This is related to the fact that the increase in Λ_0 with temperature is less than linear. Although initially the increase in Λ_0 with temperature exceeds the decrease in viscosity so that $\Lambda_0\eta$ increases, a temperature is eventually reached at which the viscosity change outweighs the conductance change, and $\Lambda_0\eta$ subsequently decreases. It is possible, moreover, that the macroscopic, bulk viscosity of solvents of this type with large molecules, in no way represents the viscosity in the neighbourhood of the ions of tetra-alkylammonium picrates, and that Walden's rule, using this observed viscosity, cannot therefore be applied.

The behaviour of tribenzylammonium and aniline picrates in the two phosphoric esters is similar to that in acetonitrile [9] and other solvents. The values of Λ_0 for the two solutes in both solvents, obtained from the Fuoss plots, are very low. This suggests that, as in a number of other solvents, the behaviour of both these picrates in the two phosphoric esters is governed largely by an acid–base, *i.e.*, molecular, dissociation in addition to a small ionic dissociation.

Much more information is required to explain the conductance relations in solvents with large molecules, and further work is in progress.

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LONDON, E.1. [*Received, April 24th*, 1957.]

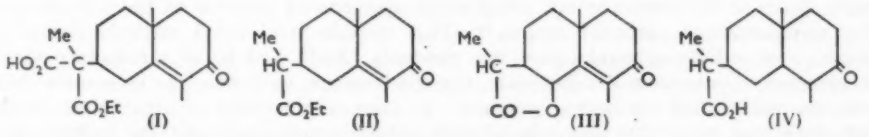
1012. *Synthetic Studies in the Santonin Series.*

By J. R. MAHAJAN, P. DUTT, and P. C. DUTTA.

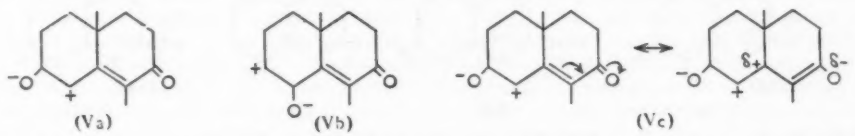
Synthesis of a dihydrosantonin related to santonin C is described, along with studies of new methods designed for synthesis of other isomers.[1]

A PREVIOUS paper [2] reported the synthesis of an isomer of a dihydrosantonin related to santonin D. The present paper reports synthesis of a dihydrosantonin related to santonin C, and related exploratory experiments designed to develop new routes to other isomers.

The half-ester [3] (I) was thermally decarboxylated to the ester [2,3] (II) which was converted, as in previous work,[2] into a mixture (III) of dihydrosantonins C and D. Attempts to obtain a pure component by heating the mixture [4] with collidine having failed, dihydrosantonin D and a smaller amount of its C isomer were separated by laborious fractional crystallisation. The structure of the former was established by bromination and dehydrobromination to santonin C, and identity was established by direct comparison with an authentic sample [3] through the kindness of Dr. Abe. Catalytic reduction of dihydrosantonin D led to an acid [5] (IV) and a trace of a neutral material.



Attempts were next directed to synthesise dihydrosantonins related to santonin A and B containing an axial propionic acid residue and *cis*-lactone ring.[6] For this purpose, advantage was taken of the diaxial [7] opening of an epoxide with the anion of ethyl methylmalonate, leading to the possibility of the formation of a γ-lactone.[8] Our interest in the present investigation centred round the unsaturated epoxide (IX), which could undergo displacement reactions with nucleophilic reagents through one of the polar forms (Va and b). The former would not be energetically favoured because polarisation of the αβ-unsaturated carbonyl group would place two positive charges on vicinal carbon atoms



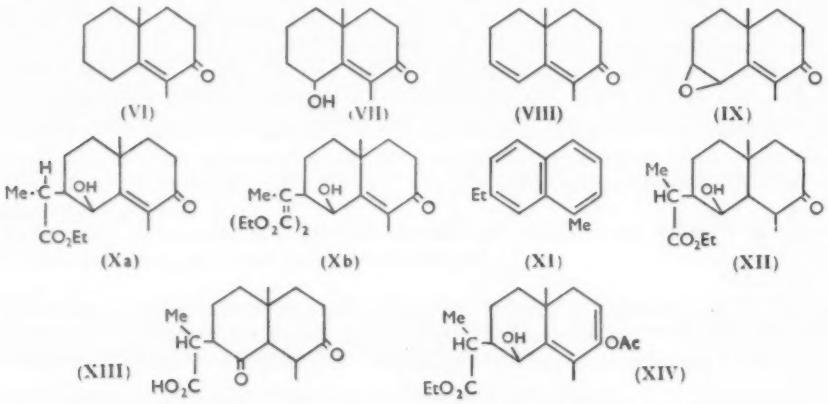
(see Vc). Consequently the form (Vb) should take part in the reaction, affording the esters (Xa and b).* Steric considerations [10] also favour the attachment of the chain at $C_{(7)}$ because of the presence of the 1-methyl group. The isolation of the hydroxy-ester (Xa)

* Van Tamelen *et al.*[9] condensed ethyl methylmalonate with 3 : 4-dihydronaphthalene 1 : 2-oxide with a view to synthesising hyposantonin, but this led to the *trans*-lactone of the β-hydroxy-α-carboxylic acid. The resonance hybrid (analogous to Va) took part in this reaction because of the participation of π-electrons in stabilising the incipient positive charge.

[1] For a preliminary communication see *Chem. and Ind.*, 1955, 170.
[2] Chakrabarti, Dutt, and Dutta, *J.*, 1956, 4978.
[3] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1416.
[4] Cocker and McMurry, *J.*, 1955, 4430.
[5] Cf. Barton and Elad, *J.*, 1956, 2085, 2090.
[6] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1953, **75**, 2567.
[7] Cookson, *Chem. and Ind.*, 1954, 1512.
[8] Traube and Lehman, *Ber.*, 1901, **34**, 1977.
[9] Van Tamelen, Van Zyl, and Zuidema, *J. Amer. Chem. Soc.*, 1950, **72**, 488.
[10] Brown and Eldred, *ibid.*, 1949, **71**, 445.

from the reaction mixture and the poor tendency exhibited by it or the related hydroxy-acid to lactonise under thermal conditions [11] ruled out the possibility of isolating the isomeric dihydrosantonins with a *trans*-fusion of the lactone-ring and involving two vicinal axial bonds. This also appeared to be improbable from steric considerations as the *cyclo*hexane ring in the bicyclic compound would preferably not exist in an energetically less favoured boat configuration.[12]

For synthesis of the esters (X), a considerable quantity of the doubly unsaturated ketone [13] (VIII) was needed. The ketone [2,13] (VI) was converted into the enol acetate and then oxidised with monoperphthalic acid. The resulting epoxide was converted by potassium carbonate in refluxing aqueous methanol into the hydroxy-ketone (VII) which was dehydrated by a catalytic amount of toluene-*p*-sulphonic acid in boiling benzene to the ketone (VIII). Perbenzoic acid in chloroform or monoperphthalic acid in ether then afforded the epoxide (IX) in a moderate yield. In analogy with well-known cases,[14] it is assumed that the $\gamma\delta$-double bond was epoxidised and this was confirmed by disappearance of ultraviolet absorption at longer wavelengths and appearance of the characteristic absorption of the $\alpha\beta$-unsaturated carbonyl group. Attempts to isolate the analytically pure epoxide (IX) by distillation or crystallisation failed but the final product was 85—90% pure as estimated by analysis and by the intensity of the ultraviolet absorption, account being taken of the hypsochromic effect of the oxygenated function at the γ-position to the $\alpha\beta$-unsaturated carbonyl system.[15] This epoxide with ethyl methylmalonate in presence of sodium ethoxide gave two products (Xa [16] and b) in satisfactory yield: in presence of potassium *tert.*-butoxide, the condensation gave only the monoester (Xa), with an unidentified low-boiling product. To confirm the point of attachment of the side-chain, the ester (Xa) was reduced with sodium borohydride, and the hydroxy-acid obtained on hydrolysis of the reduced acid was dehydrogenated with selenium: this afforded 7-ethyl-1-methylnaphthalene (XI) as expected.



It was expected that under more vigorous acidic conditions the hydroxy-ester (Xa) could perhaps lactonise with inversion, thus forming a dihydrosantonin corresponding to santonin A or B. However, it gave the ketone (VIII), arising by elimination of the axial propionic acid residue and of the hydroxyl group. The hydroxy-ester (Xa) was

[11] Newman and Vanderwerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.
[12] Cocker and McMurry, *Chem. and Ind.*, 1954, 1199.
[13] Gunstone and Heggie, *J.*, 1952, 1437.
[14] (*a*) Karrer and Sturzinger, *Helv. Chim. Acta*, 1946, **29**, 1829; (*b*) Narres, Schwarzkopf, and Lewis, *ibid.*, 1947, **30**, 880.
[15] Amendolla, Rasenkranz, and Sondheimer, *J.*, 1954, 1227.
[16] Skinner, Stokes, and Spiller, *J. Amer. Chem. Soc.*, 1947, **69**, 3083.

then reduced catalytically and the hydroxy-acid corresponding to the reduced ester (XII) was subjected to vigorous acid treatment, but it failed to yield any lactonic material.

In connection with the synthesis of naturally occurring santonins, the importance of the diketo-acid (XIII), which was isolated in an extremely poor yield and characterised through a yellow dinitrophenylhydrazone, has already been indicated.[17,18] Experiments with dihydrosantonin D (III) and the hydroxy-ester (Xa), for their eventual conversion into this diketo-acid (XIII), were without success. Attempts to shift the αβ-unsaturated linkage by formation of a ketal with ethylene glycol or ethyl orthoformate failed.[19] The lactone (III) with potassium *tert.*-butoxide did not give a useful product, and the hydroxy-ester (Xa) afforded an isomeric ester with retention of the αβ-unsaturated linkage. Attempts to oxidise the hydroxy-ester (Xa) with manganese dioxide,[15] *N*-bromosuccinimide,[20] and the chromic acid–pyridine complex [21] also failed. Refluxing the ketone (Xa) with acetyl chloride and acetic anhydride yielded the enol acetate (XIV) [characterised by $\lambda_{max.}$ 280 mμ (log ε 4·32) in hexane and by slow formation of the dinitrophenylhydrazone corresponding to (Xa)]. The extremely inert nature of the hydroxyl group in this compound (Xa) was evidently due to steric hindrance, which was indeed evident in models.

Experimental

Dihydrosantonins C, D (III).—The half-ester (I) (135 g.), obtained from the Michael condensation product, was decarboxylated at 190—195° for 1 hr., giving the ester (II), b. p. 165—170°/0·6 mm. (88 g.). This was converted into the enol acetate (95 g.) when refluxed under nitrogen with acetyl chloride (350 c.c.) and acetic anhydride (350 c.c.) for 3 hr. This acetate was oxidised with cold ethereal monoperphthalic acid, and a crude epoxide (91 g.) was obtained. This (30 g.) was converted into a mixture of dihydrosantonins (*ca.* 6 g.), m. p. 114—120°, which on fractional crystallisation from ethyl acetate and then methanol gave dihydrosantonin D[3] (3 g.), m. p. 136—137°. The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethyl acetate as orange-red needles, m. p. 250—251° (Found: C, 59·0; H, 5·6. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6%).

From the mother-liquor, a fraction of m. p. 110—115° was obtained, which on repeated crystallisation from methanol afforded *dihydrosantonin C* (0·5 g.), m. p. 125° (mixed m. p. with dihydrosantonin D 111—114°) (Found: C, 72·7; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·0%). The 2 : 4-*dinitrophenylhydrazone* separated as orange-yellow needles (from chloroform–ethyl acetate), m. p. 236—237° (Found: C, 59·1; H, 5·8. $C_{21}H_{24}O_6N_4$ requires C, 58·9; H, 5·6%). Its monobromo-derivative melted at 144° (lit., 143°). This was dehydrohalogenated by collidine: santonin C, on crystallisation from methanol, had m. p. and mixed m. p. 178—179°.

α-(*Decahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)*propionic Acid* (IV).—Dihydrosantonin D (2 g.) in dry acetone (12 c.c.) was hydrogenated in presence of palladium–strontium carbonate (100 mg.). Absorption (2 mols.) was complete in 40 min. After removal of the catalyst and solvent, the residue was taken up in ether and the acid removed in 5% sodium carbonate solution. Acidification afforded isomer acids (1·8 g.). Repeated crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) and finally from ethyl acetate afforded the pure *acid*, m. p. 120—121° (Found: C, 71·0; H, 9·6. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%). A small amount of the neutral material was repeatedly crystallised from ether–light petroleum and melted at 162—163°. Tahara [18a] described a tetrahydrosantonin having a *cis*-lactone ring and melting at 162—163°, but direct comparison was not possible.

1-*Hydroxy*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxonaphthalene* (VII).—The ketone (VI) (30 g.), acetyl chloride (120 c.c.), and acetic anhydride (120 c.c.) were refluxed under nitrogen for 6 hr. The enol acetate (32·3 g.), b. p. 120—125°/2 mm., $\lambda_{max.}$ 238 mμ (log ε 4·2 in EtOH), was oxidised with cold ethereal 0·63N-monoperphthalic acid (525 c.c.) for 24 hr. The solution was repeatedly washed with 10% sodium carbonate solution, and the solvent was

[17] (*a*) Dutta, *Science and Culture*, 1953, **19**, 164; (*b*) Dutta and Ghosh, *J. Indian Chem. Soc.*, 1955, **32**, 741.
[18] (*a*) Tahara, *J. Org. Chem.*, 1956, **21**, 442; (*b*) Cocker and McMurry, *J.*, 1956, 4549.
[19] Sondheimer, Mancera, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5020.
[20] Fieser, Herz, Klohs, Romero, and Utne, *ibid.*, 1952, **74**, 3309.
[21] Poos, Arth, Beyler, and Sarett, *ibid.*, 1953, **75**, 422.

removed. The residue was refluxed under nitrogen with potassium carbonate (20 g.) in water (180 c.c.) and methanol (900 c.c.) for 0·5 hr., then cooled and neutralised with acetic acid. Methanol was removed from a boiling-water bath. The product was diluted with water and extracted with ether. On removal of the solvent, the *hydroxy-ketone* boiled at 140—145°/3 mm. (18 g.) and had $\lambda_{max.}$ 249 mμ (log ε 3·9 in EtOH) (Found: C, 74·0; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·2%). The 2 : 4-*dinitrophenylhydrazone* melted at 214—215° alone or mixed with the derivative from the ketone (VIII) (see below).

2 : 3 : 4 : 5 : 6 : 10-*Hexahydro*-1 : 10-*dimethyl*-2-*oxonaphthalene* (VIII).—A solution of the hydroxy-ketone (25 g.) in dry benzene (400 c.c.) containing toluene-*p*-sulphonic acid (4 g.) was refluxed and water formed during the reaction was separated continuously. The doubly unsaturated ketone (16 g.) was obtained with b. p. 120—125°/3 mm., $\lambda_{max.}$ 286 mμ (log ε 4·1 in EtOH). The 2 : 4-dinitrophenylhydrazone melted at 215—216° alone or mixed with an authentic sample (Found: N, 15·7. $C_{18}H_{20}O_4N_4$ requires N, 15·7%).

Ethyl α-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)-*propionate* (Xa) *and* -*methylmalonate* (Xb).—To the ketone (VIII) (10 g.) in chloroform (20 c.c.), cooled in ice, was added a chloroform solution of perbenzoic acid (68 c.c.; 0·66N) and the whole was kept overnight, and repeatedly washed with an ice-cold 10% sodium carbonate solution and finally water. After removal of the solvent, a fraction (3·4 g.), b. p. 120—124°/1 mm., $\lambda_{max.}$ 244 mμ (log ε 3·9 in EtOH), corresponded to the epoxide (IX).

(*a*) Sodium (4·9 g., 1·2 atom-equivs.) was dissolved in alcohol (100 c.c.), and ethyl methylmalonate (90 g., 3 mols.) was added, and then the epoxide (34 g.). The mixture was kept overnight at room temperature, acidified, diluted with water, and extracted with ether. The ethereal extract was washed with 10% sodium carbonate solution, water, and very dilute hydrochloric acid. Distillation gave fractions (i) b. p. 145—150°/0·8 mm. (2 g.), (ii) b. p. 185—195°/0·8 mm. (16 g.) (Xa), and (iii) b. p. 210—215°/0·8 mm. (10 g.) (Xb). Fraction (ii), on redistillation, gave the *ester*, b. p. 168—172°/0·1 mm., $\lambda_{max.}$ 247 mμ (log ε 4·0 in EtOH) (Found: C, 69·3; H, 8·5. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·8%). Its 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as red needles, m. p. 127° (Found: C, 58·3; H, 6·5. $C_{23}H_{30}O_7N_4$ requires C, 58·2; H, 6·3%). Fraction (iii), on redistillation, gave *ester* (Xb), b. p. 200—205°/0·5 mm. (Found: C, 65·8; H, 7·9. $C_{20}H_{30}O_6$ requires C, 65·5; H, 8·1%).

(*b*) To a solution of potassium *tert.*-butoxide [from potassium (5·1 g., 0·5 atom-equiv.) in *tert.*-butyl alcohol (250 c.c.)] was added ethyl methylmalonate (136 g., 3 mols.). After 0·5 hr., the epoxide (50 g.) was added and the mixture was refluxed in nitrogen for 4 hr., then cooled in ice, acidified with dilute hydrochloric acid, and extracted with ether. On distillation it afforded fractions, b. p. 140—160°/0·6 mm. (6·5 g.) and 165—185°/ 0·6 mm. (6·5 g.). The second fraction corresponded to the ester (Xa) (Found: C, 69·0; H, 8·7%) (dinitrophenylhydrazone, m. p. 126°). The first fraction redistilled at 140—145°/0·1 mm., had $\lambda_{max.}$ 248 mμ (log ε 3·9 in EtOH) (Found: C, 72·3, 72·5; H, 8·4, 8·4%), and gave no dinitrophenylhydrazone.

7-*Ethyl*-1-*methylnaphthalene* (XI).—The hydroxy-ester (Xa) (0·82 g.) was reduced with sodium borohydride (110 mg.) in methanol (2 c.c.). The dihydroxy-ester (0·8 g.) was hydrolysed with potassium hydroxide (0·64 g.) in methanol (6 c.c.) and water (1 c.c.) on the water-bath for 4 hr. The acidic product (0·6 g.) was dehydrogenated with selenium (3 g.) at 300—350° for 40 hr. in a sealed tube. The hydrocarbon, isolated in the usual way and distilled over sodium, was directly converted into a picrate, orange-yellow needles (from methanol), m. p. 95° alone or mixed with that (m. p. 96—97°) of 7-ethyl-1-methylnaphthalene.

Reactions of the Hydroxy-ester (Xa).—(a) *With hydrochloric–acetic acid.* The hydroxy-ester (3 g.) was refluxed in nitrogen with acetic acid (20 c.c.), concentrated hydrochloric acid (20 c.c.), and water (20 c.c.) for 12 hr. The dark brown solution was diluted with water and extracted with ether. The ethereal extract was washed with water, ice-cold dilute 5% potassium hydroxide solution, and water, and dried (Na_2SO_4). On removal of the solvent, the residue was distilled, the major fraction distilling at 120—125°/1·5 mm. Its 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark-red shining flakes, m. p. 214—215° alone or mixed with the derivative of the ketone (VIII) (Found: N, 15·6. Calc. for $C_{18}H_{20}O_4N_4$: N, 15·7%).

(b) *With potassium in* tert.-*butyl alcohol.* The hydroxy-ester (1 g.) was refluxed in nitrogen with a solution of potassium (1 g.) in *tert.*-butyl alcohol (50 c.c.) for 8 hr. The mixture was acidified with acetic acid, and after removal of the solvent was treated with hydrochloric acid and extracted with ether. The ether solutions gave on evaporation a residue which was refluxed

on the water-bath with potassium hydroxide (2 g.) in methanol (20 c.c.) and water (5 c.c.) for 3 hr. The acidic material was isolated in the usual way and esterified with diazomethane. The methyl ester had b. p. 180°/1 mm. $\lambda_{max.}$ 247 mμ (log ε 3·9 in EtOH). This was converted into a 2 : 4-*dinitrophenylhydrazone*, orange flakes (from ethyl acetate) or red needles (from benzene–ethyl acetate), m. p. 190—191°, $\lambda_{max.}$ 390 mμ (log ε 4·3 in EtOH) (Found: C, 57·1; H, 6·1. $C_{22}H_{28}O_7N_4$ requires C, 57·3; H, 6·0%).

Ethyl α-(*Decahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthyl*)*propionate* (XII).—The hydroxy-ester (Xa) (2 g.) was slowly hydrogenated in acetic acid (15 c.c.) in presence of platinic oxide (100 mg.). The *product* distilled at 170—175°/0·2 mm. (Found: C, 68·7; H, 9·0. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·4%). It readily formed a yellow dinitrophenylhydrazone, which melted over a wide range.

Ethyl α-(7-*Acetoxy*-1 : 2 : 3 : 4 : 5 : 10-*hexahydro*-1-*hydroxy*-8 : 10-*dimethyl*-2-*naphthyl*)-*propionate* (XIV).—The hydroxy-ester (0·5 g.) was refluxed in nitrogen with acetyl chloride (2 c.c.) and acetic anhydride (5 c.c.) for 1·5 hr. Low-boiling products were removed at a water-pump. The residual *ester* (XIV) was taken up in ether, washed with 2% sodium carbonate solution, and distilled. It boiled at 180°/0·5 mm. (Found: C, 67·9; H, 8·2. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·3%). It afforded the dinitrophenylhydrazone of (Xa) when kept for 0·5 hr. at room temperature with a solution of the reagent.

Analyses were carried out by Mrs. Chhabi Dutta at the Micro-analytical Laboratory of the University College of Science, Calcutta. Thanks are also recorded for a gift of chemicals from the East India Pharmaceutical Works Ltd., Calcutta.

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1013. *ω-Halogenomethyl-pyridines, -quinolines, and* -isoquinolines. *Part VII.** αβ-*Di-2′-quinolylacrylic Acid.*

By D. Ll. Hammick, E. Johnston, and E. D. Morgan.

The new compound, αβ-di-2′-quinolylacrylic acid, has been prepared in good yield by a Perkin synthesis and found to have the quinolyl groups in the unexpected *trans*-relation. Decarboxylation of the acid gives *trans*-1 : 2-di-2′-quinolylethylene.

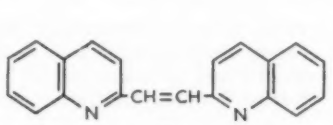
In studies of 1 : 2-di-2′-quinolylethylene (I) in this laboratory, the *cis*-isomer has been prepared by irradiation of the stable *trans*-form with ultraviolet light.[1] However, the method is not suitable for large-scale working. Since decarboxylation of α-phenylcinnamic acid with copper chromite is known to give *cis*-stilbene,[2] it was hoped that decarboxylation of the hitherto unknown, analogous quinolyl compound, αβ-di-2′-quinolylacrylic acid (II) might produce *cis*-1 : 2-di-2′-quinolylethylene. Ruggli and Staub[3] have shown that condensation of substituted benzaldehydes with phenylacetic acid gives α-phenylcinnamic acids with the phenyl groups *cis* to each other, and Stephenson[4] has obtained similar results with fluorenylacetic acids. Further, Curtin and Harris[5] have shown that configuration is retained during decarboxylation with copper chromite. However, in the present case the condensation did not take the same course: the acid (II) was found to have the *trans*-configuration and gave the *trans*-ethylene on decarboxylation.

Ethyl 2-quinolylacetate and quinoline-2-aldehyde were required as intermediates. The recorded methods of preparing the ester[6] were found to give yields of less than 10%;

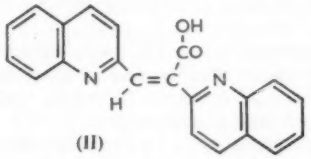
* Part VI, *J.*, 1957, 1533.

[1] Hammick, Lammiman, Morgan, and Roe, *J.*, 1955, 2436.
[2] Taylor and Crawford, *J.*, 1934, 1130.
[3] Ruggli and Staub, *Helv. Chim. Acta*, 1936, **19**, 1288.
[4] Stephenson, *J.*, 1949, 655.
[5] Curtin and Harris, *J. Amer. Chem. Soc.*, 1951, **73**, 2716, 4519.
[6] Cf. Clemo and Nath, *J.*, 1952, 2197.

we have now prepared it in a new way from quinaldinyl-lithium and ethyl carbonate in 60% yield, based on unrecovered quinaldine. The usual preparation of quinoline-2-aldehyde, by oxidation of quinaldine with selenium dioxide, is unpleasant and gives several by-products; hydrolysis of dibromoquinaldine [7] is intrinsically better but sometimes



(I)



(II)

the aldehyde polymerizes in the alkaline conditions of its isolation. We have improved the latter method to give reliably good yields. Ethyl 2-quinolylacetate and quinoline-2-aldehyde, thus prepared, were condensed in the presence of piperidine; hydrolysis of the resulting acrylic ester gave αβ-di-2′-quinolylacrylic acid (II).

As in the case of the diquinolylethylenes,[1] it can be shown that if the quinolyl groups of the acrylic acid and its ester are *cis* to each other then their electron systems will not be conjugated and the ultraviolet spectrum of the molecule will resemble that of quinoline or *cis*-diquinolylethylene. When the groups are *trans*, then conjugation is possible and there will be an entirely different ultraviolet spectrum, resembling that of *trans*-diquinolylethylene. The intense ultraviolet absorption of both the diquinolylacrylic acid [$\lambda_{max.}$ 2700 and 3450 Å (ε 34,740 and 34,120)] and its ethyl ester [$\lambda_{max.}$ 2720 and 3475 Å (ε 49,420 and 24,500)], as prepared here, showed that the quinolyl groups in both compounds were in the planar, conjugated, *trans*-position. Attempts to isomerize both the acid and the ester by ultraviolet irradiation or by refluxing them in nitrobenzene with a trace of iodine were unsuccessful. Decarboxylation of the acid (II) at 125—130° gave only the stable *trans*-ethylene, *i.e.*, configuration was retained during decarboxylation.

Experimental

Ethyl 2-Quinolylacetate.—Dry bromobenzene (53 ml., 0·5 mole) was added, with stirring, to lithium (7 g., 1 g.-atom), cut into small pieces, under dry ether (400 ml.) in a 1-l. flask, at a rate sufficient to keep the mixture refluxing. When practically all the lithium had dissolved, freshly distilled quinaldine (68 ml., 0·5 mole; dried over potassium hydroxide) was added every 15 min., the mixture was then refluxed for 15 min., to give a deep red solution of quinaldinyl-lithium.

Freshly distilled diethyl carbonate (29·5 g., 0·25 mole) was added during 30 min., and the mixture stirred at room temperature for 3 hr. Then the product was cooled in an ice-bath and carefully acidified with 3N-hydrochloric acid. The aqueous layer was removed, and the ether layer shaken with more 3N-hydrochloric acid. The combined aqueous portions were neutralized with solid sodium carbonate, and the liberated oil was extracted with ether. The ether extract was dried, and the ether removed; the residue was distilled through a short fractionating column. Fraction (*a*), b. p. 65—100°/0·7 mm., was identified as quinaldine (35·6 g., 49% recovery); fraction (*b*), b. p. 128—135°/0·8 mm., gave analyses correct for ethyl 2-quinolylacetate (32·5 g., 60% on unrecovered quinaldine) (Found: C, 72·3; H, 5·9; N, 6·6. Calc. for $C_{13}H_{13}O_2N$: C, 72·55; H, 6·0; N, 6·5%) and formed a yellow picrate (from ethanol), m. p. 148—150° (decomp.). Borsche and Manteufel [8] report a picrate, m. p. 150—152°. Higher-boiling material (2·5 g.), b. p. 135—175°/0·8 mm., appeared to be chiefly 1 : 2-dihydro-2-methyl-2-phenylquinoline, m. p. 90—91°, formed by the addition of phenyl-lithium to quinaldine.

Quinoline-2-aldehyde.—Dibromoquinaldine [9] (12 g.) was dissolved in boiling ethanol (100 ml.) and treated with silver nitrate (17·2 g.) in boiling water (20 ml.) and refluxed for 10 min. Concentrated hydrochloric acid was added to precipitate excess of silver, and the mixture of silver

[7] Hammick, *J.*, 1926, 1302.
[8] Borsche and Manteufel, *Annalen*, 1936, **526**, 25.
[9] Sharp, *J. Pharm. Pharmacol.*, 1949, **1**, 395.

halides was filtered from the hot solution. The ethanol was removed from the acid solution by steam-distillation. The residue from the steam-distillation was cooled in ice and neutralized with calcium carbonate. The yellow solid which separated was filtered off, dried in a desiccator, and crystallized from light petroleum (b. p. 60—80°), to give quinoline-2-aldehyde (5·3 g., 85%), m. p. 70—71°. Hammick [7] gives m. p. 71°.

Ethyl αβ-Di-2′-quinolylacrylate.—Quinoline-2-aldehyde (3·14 g., 0·02 mole) and ethyl 2-quinolylacetate (4·3 g., 0·02 mole) in ethanol (50 ml.) and piperidine (2 ml.) were refluxed for 12 hr., then cooled in ice. The solid which formed was recrystallized from ethanol, to give white needles of *ethyl αβ-di-2′-quinolylacrylate* (3·8 g., 54%), m. p. 143° (Found: C, 77·8; H, 5·1; N, 7·75. $C_{23}H_{18}O_2N_2$ requires C, 77·9; H, 5·1; N, 7·9%).

αβ-Di-2′-quinolylacrylic Acid.—Ethyl αβ-di-2′-quinolylacrylate (3·54 g.) was dissolved in warm ethanol (60 ml.) and added to potassium hydroxide (6 g.) in water (60 ml.). The mixture was gently refluxed for 20 min., then poured into water (500 ml.) and adjusted to pH 7 with dilute hydrochloric acid. After filtration and drying, the precipitate which was formed recrystallized from chloroform, to give colourless needles of *αβ-di-2′-quinolylacrylic acid* (2·5 g., 75%), m. p. 169° (decomp.) (Found: C, 77·1; H, 4·4. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3%).

Decarboxylation of αβ-Di-2′-quinolylacrylic Acid.—αβ-Di-2′-quinolylacrylic acid (0·5 g.) was heated in freshly distilled quinoline (5 ml.) with copper chromite (0·1 g.) at 130° until no more carbon dioxide was evolved (20 min.). The hot mixture was filtered and the filtrate diluted with ethanol (20 ml.). Dropwise addition of water precipitated a solid product which crystallized from benzene–methanol (1 : 1), to give *trans*-(β)-1 : 2-di-2′-quinolylethylene (0·37 g., 80%), m. p. 188—190°, undepressed on admixture with an authentic specimen.

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1014. *Thiohydantoins. Part I. Ionisation and Ultraviolet Absorption.*

By J. T. EDWARD and S. NIELSEN.

Absorption spectra of variously substituted 2-thiohydantoins in ethanol, water, and aqueous sodium hydroxide have been determined. Ionisation of 2-thiohydantoins in alkaline solution leads to characteristic changes in absorption, which may be used for distinguishing 1- from 3-substituted 2-thiohydantoins. They are also distinguishable by their pK_a' values.

INCREASING use is made of procedures in which the *N*-terminal [1] or *C*-terminal [2] amino-acid residues of polypeptides are detached as 2-thiohydantoin derivatives. In this connection we have examined the ultraviolet absorption of various thiohydantoins. It is already known [3–5] that they have a strong absorption band in the region 260—270 mμ (main peak) and a band, usually weaker, at 220—230 mμ (subsidiary peak), but no detailed studies have been made of the effect on absorption of changes in structure.

In Table 1 are given the absorption characteristics of twenty-one thiohydantoins. It is evident that a change in solvent from ethanol to water results in small shifts of one or both peaks. Because of low solubilities in water, the spectra of some compounds were determined in water containing 10% (v/v) of ethanol; these should be almost the same as the spectra in water (cf. Table 2).

Substitution of the 2-thiohydantoin nucleus by alkyl groups at $N_{(1)}$ or $N_{(3)}$ causes small bathochromic shifts in the subsidiary peak. Substitution by a phenyl group at $N_{(1)}$ causes a bathochromic shift of 10—17 mμ in both peaks, but at $N_{(3)}$ is without appreciable

[1] *Ann. Reports*, 1953, **50**, 275.
[2] *Ibid.*, 1955, **52**, 277.
[3] du Vigneaud and Melville, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, pp. 269 *et seq.*
[4] Carrington and Waring, *J.*, 1950, 354.
[5] Kjaer and Erikson, *Acta Chem. Scand.*, 1952, **6**, 448; Dahlerup-Petersen, Linderstrøm-Lang, and Ottesen, *ibid.*, p. 1135; Jeffreys, *J.*, 1954, 2221.

TABLE 1. *Absorption characteristic of substituted 2-thiohydantoins in different solvents.*

Substituent	Ethanol $\lambda_{max.}$ (mμ) *	Ethanol $\varepsilon_{max.}$	Water $\lambda_{max.}$ (mμ) *	Water $\varepsilon_{max.}$	Aqueous NaOH † $\lambda_{max.}$ (mμ) *	Aqueous NaOH † $\varepsilon_{max.}$
(2-Thiohydantoin) [a]	264	17,000	259	16,700	260	24,300 [r]
	222	9,100	223	9,500	214	4,000
1-Methyl [b]	265	15,300	261	14,000	258	33,700 [r]
	230	11,400	230	13,500		
3-Methyl [c]	263	17,000	259	15,800	—	—[r]
	232	10,000	235	11,900		
5-Methyl [d]	266	17,600	261	16,700	259	24,600 [r]
	224	8,400	224	9,800	210	5,000
5-*iso*Propyl [e]	266	20,100	262	17,400	260	25,900
	226	8,900	226	8,800		
1-Phenyl [f]	281	11,300	269	11,100	263	25,500 [r]
	236	17,200	235	23,500		
3-Phenyl [g]	266	14,600	262	14,700	—	—[r]
	(229	8,400)	229	8,700		
5-Phenyl [h]	270	18,100	271	15,300 [p]	271	20,500 [r]
	(228	9,100)	234	8,400 [p]		
5-Benzyl [i]	267	18,200	264	16,900	—	—[r]
	224	7,500	225	8,500		
1 : 3-Dimethyl [c, j]	265	13,500	261	11,900	—	—[r]
	239	12,800	239	16,500		
3 : 5-Dimethyl [c]	265	14,900	263	14,800	—	—[r]
	233	8,500	235	9,500		
5 : 5-Dimethyl [k]	266	17,800	262	16,500	259	23,000
	223	8,700	223	9,600	210	6,000
5 : 5-Pentamethylene [k]	267	19,400	263	18,500	259	24,200
	224	8,400	224	10,300		
1-Methyl-3-phenyl [j]	267	14,000	261	12,800	—	—[r]
	232	10,400	236	11,800		
3-Ethyl-1-phenyl [l]	279	10,200	269	10,300 [p]	—	—[r]
	244	16,000	245	16,700 [p]		
1 : 3-Diphenyl [f]	280	11,700 [q]	278	11,300	378	8,070 [s]
					(278	8,300) [s]
3 : 5-Diphenyl [m]	271	17,600	269	12,900	—	—[r]
	(266	17,000)				
5 : 5-Diphenyl [n]	272	21,500	270	20,300 [p]	266	26,500
	(233	10,100)	(235	9,400) [p]		
3 : 5 : 5-Trimethyl [c]	265	17,300	262	17,000	258	5,000 [t]
	231	9,000	235	10,700	224	16,900 [t]
1-Methyl-5 : 5-pentamethylene [k]	266	19,000	262	16,100	255	27,800
	230	10,700	231	12,700	218	4,800
3-Methyl-5 : 5-pentamethylene [k]	266	16,500	264	14,900	259	5,000 [t]
	233	8,500	235	9,600	223	15,600 [t]

* Inflexions in parentheses.

[a] Johnson and Nicolet, *J. Amer. Chem. Soc.*, 1911, **33**, 1973. [b] Elmore, Ogle, and Toseland, *J.*, 1956, 192. [c] Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3278. [d] Johnson, *J. Biol. Chem.*, 1912, **11**, 97. [e] Jackman, Klenk, Fishburn, Tullar, and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 2884. [f] Wheeler and Brautlecht, *Amer. Chem. J.*, 1911, **45**, 446. [g] Aschan, *Ber.*, 1884, **17**, 420; Edman, *Acta Chem. Scand.*, 1950, **4**, 277. [h] Swan, *Austral. J. Sci. Res.*, 1952, **5**, *A*, 711. [i] Delépine, *Bull. Soc. chim. France*, 1903, **29**, 1198. [j] Cook and Cox, *J.*, 1949, 2342. [k] Carrington, *J.*, 1947, 684. [l] Brooker, Keyes, Sprague, Van Dyke, Van Lane, Van Zandt, and White, *J. Amer. Chem. Soc.*, 1951, **73**, 5326. [m] Kossel, *Ber.*, 1891, **24**, 4145. [n] Biltz, *Ber.*, 1909, **42**, 1792,

[p] Solvent was 9 : 1 (v/v) H_2O–EtOH. [q] Solution (4 ml.) acidified with one drop of conc. HCl. [r] Rapid hydrolysis indicated by disappearance of main peak; absorption characteristics, where given, obtained by extrapolation.

† Concentration 0·01N, except for: [s] 0·001N; [t] 1N.

TABLE 2. *Ultraviolet absorption of 5 : 5-dimethyl-2-thiohydantoin in various concentrations of aqueous ethanol.*

EtOH (% v/v)	100	90	70	50
$\lambda_{max.}$ (mμ) ($\varepsilon_{max.}$)	266 (17,800)	265 (18,000)	265 (18,000)	264 (18,500)
	233 (8,700)	223 (8,800)	224 (9,300)	233 (9,900)
EtOH (% v/v)	30	10	0	
$\lambda_{max.}$ (mμ) ($\varepsilon_{max.}$)	264 (17,400)	262 (17,000)	262 (16,500)	
	224 (9,700)	224 (9,600)	223 (9,600)	

effect.[6] This may be related to the fact that while the 1-phenyl group may approach coplanarity with the ·N·CS·NH·CO· chromophore by a small bending of the N–Ph bond, the 3-phenyl group is more severely hindered by the flanking carbonyl and thiocarbonyl groups (Fig. 1).[7] Substitution at $C_{(5)}$ by alkyl groups has only a minor effect on absorption; substitution by phenyl groups causes a small bathochromic shift, probably because of π–π electronic interaction across the saturated carbon atom.[8] When the phenyl group is

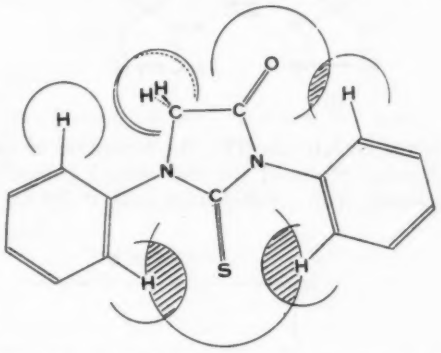


FIG. 1. *Scale drawing of* 1 : 3-*diphenyl-2-thiohydantoin, using bond-lengths and angles from crystallographic studies of related compounds* (*Corey*, J. Amer. Chem. Soc., 1938, **60**, 1598; *Davies and Blum*, Nature, 1954, **173**, 993) *and from Pauling* ("*The Nature of the Chemical Bond*," *Cornell University Press, Ithaca*, 2nd *ed.*, 1948, *pp.* 79, 160, 187); *van der Waals radii from Pauling except for hydrogen* (*Forbes and Mueller*, Canad. J. Chem., 1956, **34**, 1542; *cf. Crombie*, Quart. Rev., 1952, **6**, 101; *Braude and Sondheimer*, J., 1955, 3754).

separated from the ·NH·CS·NH·CO· chromophore by two saturated carbon atoms, as in 5-benzyl-2-thiohydantoin, its effect is slight.

In alkaline solution thiohydantoins ionise [3] but also undergo ring fission [9] at varying rates. However, the hydrolysis of the 2-thiohydantoins listed in Table 3 is so slow,[10]

TABLE 3. *Acid dissociation constants at* 18° ± 3°.

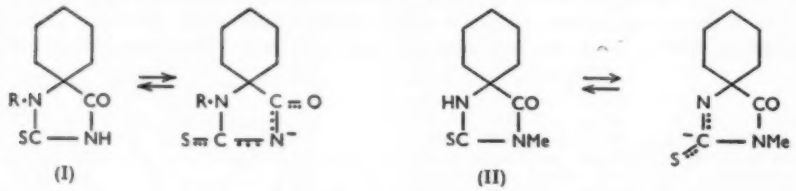
Compound	pK_a'
Hydantoin	9·16 *
5-*iso*Propyl-2-thiohydantoin	8·70
5 : 5-Dimethyl-2-thiohydantoin	8·71
5 : 5-Pentamethylene-2-thiohydantoin	8·79
5 : 5-Diphenyl-2-thiohydantoin	7·69 †
3 : 5 : 5-Trimethyl-2-thiohydantoin	10·80
1-Methyl-5 : 5-pentamethylene-2-thiohydantoin	9·25
3-Methyl-5 : 5-pentamethylene-2-thiohydantoin	11·23

* Zief and Edsall (*J. Amer. Chem. Soc.*, 1939, **61**, 423) report $pK_a' = 9·12$ at 25°.
† In 9 : 1 (v/v) H_2O–EtOH.

that the absorption characteristics of their ionised forms may be accurately determined. Ionisation at $N_{(3)}$–H, as in 1-methyl-5 : 5-pentamethylene-2-thiohydantoin (I; R = Me) results in a slight hypsochromic shift, but a big increase in intensity, of the main peak, and a hypsochromic shift and decrease in intensity of the subsidiary peak (Fig. 2). On the other hand, ionisation of $N_{(1)}$–H, as in 3-methyl-5 : 5-pentamethylene-2-thiohydantoin (II) results in a reduction of intensity of the main peak and in an increased intensity of the subsidiary peak, both at slightly shorter wavelength (Fig. 3). Thiohydantoins unsubstituted at $N_{(1)}$ and $N_{(3)}$, such as 5 : 5-pentamethylene-2-thiohydantoin (I; R = H), have in alkaline solution spectra similar in general to those of 1-substituted 2-thiohydantoins and hence must ionise, as expected,[11] at $N_{(3)}$–H.

[6] Cf. Crombie and Hooper, *J.*, 1955, 3010.
[7] Braude and Waight, "Progress in Stereochemistry," ed. Klyne, Butterworths, London, 1954, p. 126.
[8] Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 18; Baddeley, *Ann. Reports*, 1954, **51**, 167.
[9] Kenner, Khorana, and Stedman, *J.*, 1953, 673.
[10] Cf. Ingold, Sako, and Thorpe, *J.*, 1922, 1177.
[11] Pickett and McLean, *J. Amer. Chem. Soc.*, 1939, **61**, 423; Stuckey, *J.*, 1947, 331.

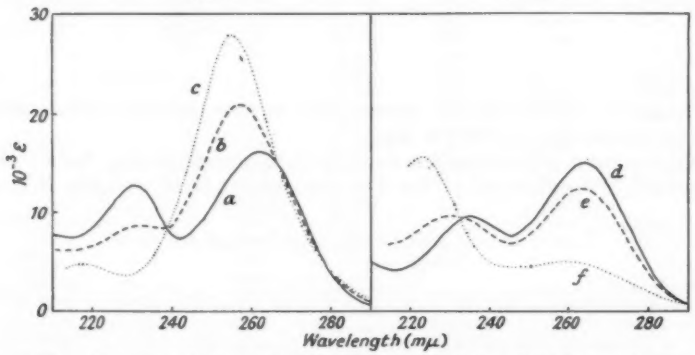
Unlike the other 1 : 3-disubstituted 2-thiohydantoins of Table 1, 1 : 3-diphenyl-2-thiohydantoin (III) proved moderately stable in very dilute sodium hydroxide solution, in which it had an absorption peak at 378 mμ (Table 1). We tentatively ascribe this peak



(I) (II)

to the enolate ion (IV), the formation of which would be assisted by the electron-withdrawing effects of the two phenyl groups.[12] Ionisation was also indicated in ethanol solution, with a well-defined peak at 390 mμ as well as a flat peak at 279 mμ; the former

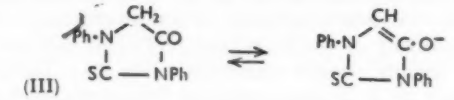
FIG. 2. FIG. 3.



FIGS. 2 *and* 3. *Absorption spectra of* 1-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (*Fig.* 2) *and* 3-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (*Fig.* 3) *in aqueous solution.*
a, *d*, pH 5·5; *b*, pH 9·21; *c*, pH 12; *e*, pH 10·73; *f*, pH 14.

peak increased in intensity with dilution [13] but disappeared completely when one drop of concentrated hydrochloric acid was added to 4 ml. of the ethanolic solution. In aqueous solution the absorption was normal (Table 1).

The apparent dissociation constants of several 2-thiohydantoins in water, and (for



(III) (IV)

solubility reasons) of 5 : 5-diphenyl-2-thiohydantoin in 10% aqueous ethanol (Table 3), were determined by the well-established spectrophotometric procedure.[14,15] The use of the latter solvent instead of water should increase the pK_a' by about 0·1.[16] It is evident

[12] van der Krogt and Wepster, *Rec. Trav. chim.*, 1955, **74**, 161; Brown, McDaniel, and Häfliger, "Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Academic Press, New York, 1953, p. 567.
[13] Cf. Gillam and Stern, "Electronic Absorption Spectroscopy," Arnold, London, 1953, p. 8.
[14] Flexser, Hammett, and Dingwall, *J. Amer. Chem. Soc.*, 1935, **57**, 2103.
[15] Butler, Ruth, and Tucker, *ibid.*, 1955, **77**, 1486.
[16] Cavill, Gibson, and Nyholm, *J.*, 1949, 2466.

that 5-alkyl-substituted 2-thiohydantoins have a pK_a' of about 8·7 in water. Values of 8·9 and 9·1 have been reported for the pK_a' of 2-thiohydantoin and 5-methyl-2-thiohydantoin, respectively, in aqueous methanol (exact concentration unspecified, but less than 50%).[3] Hence a pK_a' of about 8·5 may be expected for the former compound in water.

The acid-strengthening effect of a 5-phenyl group [12,15] and the acid-weakening effect of a 1-methyl group [17] are in accord with analogous cases in the literature.

Experimental

Absorption measurements were carried out with a Unicam S.P. 500 or Beckman DU spectrophotometer, and 1 cm. matched quartz cells. pH measurements were made with a Radiometer pH meter No. 23 and glass and calomel electrodes. The thiohydantoins were prepared by the methods described in the literature, and purified to constant m. p.; in some cases purity was checked by paper chromatography.[18] A method more convenient than those reported [19] for preparing 1-substituted 2-thiohydantoins is given below.

1-*Phenyl-2-thiohydantoin*.—The hydrochloride of *N*-phenylglycine was prepared by evaporating the water from a mixture of the amino-acid (1·5 g.) and concentrated hydrochloric acid (1 ml.). Ammonium thiocyanate (0·8 g.) was added, and the mixture heated at 155° for 15 min. The melt was warmed with 3% hydrochloric acid (3 ml.), and the solid removed. On crystallisation from ethanol it afforded 1-phenyl-2-thiohydantoin (0·9 g.), m. p. 187—189°.[20] This gave with nitroprusside–piperazine [21] the characteristic purple colour of 2-thiohydantoins unsubstituted at position 5.[18]

Measurements of Ionisation Constants.—The spectra of the thiohydantoins were determined in distilled water (pH 5·5—6); in various buffer solutions (ionic strength about 0·01M), and in sodium hydroxide solution concentrated enough to ensure complete ionisation (M for 3-substituted compounds; 0·01M for others) (cf. Figs. 2 and 3). The pK_a' values were calculated from the change in absorption values at several different wave-lengths, according to the usual procedure,[14] and averaged.

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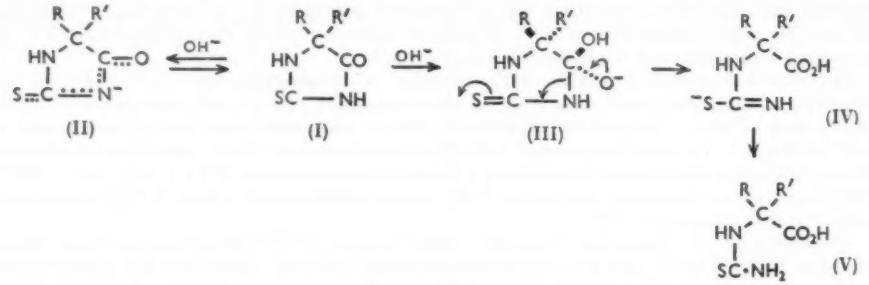
[17] Walter, Ryan, and Lane, *J. Amer. Chem. Soc.*, 1956, **78**, 5560.
[18] Edward and Nielsen, *Chem. and Ind.*, 1953, 197.
[19] Refs. *b* and *f* of Table 1; Komatsu, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1914, **1**, 69.
[20] Ref. *f* of Table 1.
[21] Edward and Waldron, *J.*, 1952, 3621.

1015. *Thiohydantoins. Part II.*[1] *Alkaline Hydrolyses.*

By J. T. Edward and S. Nielsen.

Kinetic studies indicate that the rate-determining step in the hydrolysis of 2-thiohydantoins to thioureido-acids is attack of a hydroxide ion on the un-ionised molecule. The effect of substitution of the 2-thiohydantoin ring on its rate of hydrolysis has been investigated.

In alkaline solution 5-substituted 2-thiohydantoins (I) (*a*) ionise (practically instantaneously) as weak acids to give the anions (II),[1,2] and (*b*) are hydrolysed (more slowly) to salts of the thioureido-acids (V),[3] probably *via* the intermediates (III) [4] and (IV). Because it seemed possible that the low yields [5] of 2-thiohydantoins in Schlack and Kumpf's procedure [6] for degrading proteins might be due in part to hydrolysis, we have studied the



kinetics of this reaction for variously substituted compounds. The reaction was easily followed spectrophotometrically.[7] In alkaline solution the spectra changed from those characteristic of 2-thiohydantoins to those characteristic of thioureido-acids (Figs. 1 and 2). When the solutions were made strongly acid these changes were reversed.[3] The rates of hydrolysis were obtained by following the change in optical density with time at some wavelength in the region 260—270 mμ, the exact wavelength usually being that at which the change in absorption was maximal. Because the temperatures of the cells in the spectrophotometer were not controlled precisely (see p. 5083), the rates are only approximate, and this paper attempts only a preliminary survey of the mechanism of the hydrolysis.

To eliminate the complications due to ionisation,[1] the hydrolysis of 1 : 3-disubstituted 2-thiohydantoins was first studied (Table 1). These compounds were hydrolysed extremely

Table 1. *Alkaline hydrolysis of* 1 : 3-*disubstituted* 2-*thiohydantoins.*

Substituents	1 : 3-Dimethyl				3-Ethyl-1-phenyl		1-Methyl-3-phenyl	
pH	9·74	10·84	11·32	11·64	9·82	10·78	9·82	10·78
10^3k_e (min.$^{-1}$)	0·68	8·11	33·6	50·0	1·69	14·1	3·92	24·9
k_2 (l. mole^{-1} min.$^{-1}$) ...	124	118	128	114	256	234	593	413

rapidly in dilute alkali, and the reaction could be followed conveniently only in buffer solutions. In the large excess of buffer the rate of hydrolysis v was of the first order with

[1] Part I, preceding paper.
[2] du Vigneaud and Melville, "The Chemistry of Penicillin," Princeton University Press, 1949, p. 269.
[3] Ware, *Chem. Rev.*, 1950, **46**, 403.
[4] Bender and Ginger, *J. Amer. Chem. Soc.*, 1955, **77**, 348.
[5] Waley and Watson, *J.*, 1951, 2394; Edward and Nielsen, *Chem. and Ind.*, 1953, 197.
[6] Schlack and Kumpf, *Z. physiol. Chem.*, 1926, **154**, 125.
[7] Kenner, Khorana, and Stedman, *J.*, 1953, 673.

respect to thiohydantoin; however, the second-order character of the reaction was shown by the rough proportionality of the apparent first-order rate constant, k_e, to the hydroxide-ion concentration, as required by the equations:

$$v = k_e\,[\text{Thiohydantoin}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$= k_2\,[\text{Thiohydantoin}][OH^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k_2 ($= k_e/[OH^-]$) is a second-order rate constant. The kinetics of alkaline hydrolysis of the amide linkage are generally of second order.[8]

Hydrolysis of 2-thiohydantoin (I; R = R′ = H) in dilute alkali was slower and again appeared to be of first order with respect to the stoicheiometric concentration of thiohydantoin. However, the apparent first-order rate constants were changed only slightly

FIG. 1. FIG. 2.

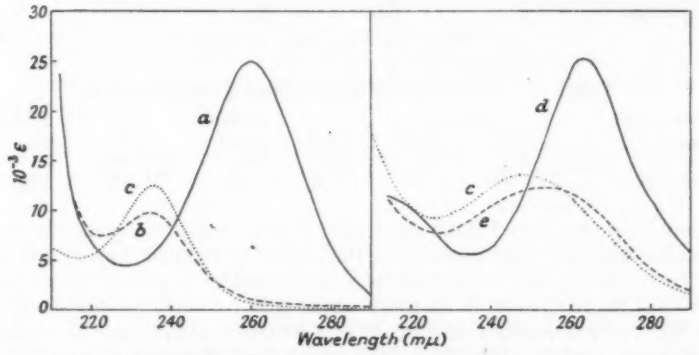


FIG. 1. *5-Methyl-2-thiohydantoin in 0·01N-sodium hydroxide immediately (curve a) and 48 hours (curve b) after mixing; thiourea (curve c) in water.*

FIG. 2. *1-Phenyl-2-thiohydantoin in 0·01N-sodium hydroxide immediately (curve d) and 24 hours (curve e) after mixing; phenylthiourea (curve c) in water.*

by a hundred-fold change in hydroxide-ion concentration (Table 2), indicating a zero order with respect to hydroxide ion. This kinetic order may be explained if it is assumed that only the un-ionised molecules (I) react with hydroxide ion.[9] The rate of hydrolysis is

TABLE 2. *Hydrolysis of 2-thiohydantoin at* 21—22°.

$[OH^-]$ (mole/l.) ...	0·02	0·05	0·05 [a]	0·05 [b]	0·10	0·20	0·50	1·00	2·00
$10^3 k_e$ (min.$^{-1}$)	1·79	1·63	1·61	1·56	1·20	1·25	1·56	1·58	1·71

Plus [KCl] = [a] 0·25; [b] 1·00 mole/l.

again given by equation (2), but the thiohydantoin concentration is that of un-ionised molecules, and not the stoicheiometric concentration. It may then be shown [9] that

$$k_e = k_2 K_w/([H^+] + K_a') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where K_w is the ionic product of water and K_a' the apparent dissociation constant for the reaction: (I) $\rightleftharpoons$ (II) + H^+. Since for the alkali concentrations of Table 2 $H^+ \ll K_a'$,[1] equation (3) simplifies to:

$$k_e = k_2 K_w/K_a' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

[8] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 784.
[9] Edward and Terry, *J.*, 1957, 3527.

whence follows the approximate independence of k_e of hydroxide-ion concentration. The small variation of k_e would then be due to the variation of K_a' with ionic strength.[10]

Taking the k_e ($1{\cdot}79 \times 10^{-2}$ min.$^{-1}$) of the most dilute solution, and assuming a pK_a' of 8·5,[1] we can calculate a value of $k_2 = 5650$ l. mole^{-1} min.$^{-1}$ from equation (4) for the hydrolysis of 2-thiohydantoin. It is thus evident that, judged by the rate of hydrolysis of its un-ionised molecule, 2-thiohydantoin is extremely reactive and that it owes its comparative stability in alkaline solution to its ionisation.

TABLE 3. pH *of an aqueous* 0·01M-*solution of* 2-*thiohydantoin on standing.*

Time (min.)	0	15	45	75	260	600	1400	2020	3000	4260
pH	(5·66)	5·12	4·89	4·79	4·41	4·26	3·98	3·82	3·70	3·70

TABLE 4. *Hydrolysis of* 1- *and* 5-*substituted* 2-*thiohydantoins.*

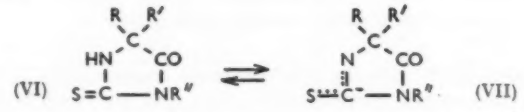
Substituent	1-Phenyl	5-Methyl	5-*iso*Propyl	5 : 5-Dimethyl
$10^4 k_e$ (min.$^{-1}$)	32 [a]	16 [b]	5·5 [b]	0·1 [b]
k_2 (l. mole^{-1} min.$^{-1}$)	201	320	110	2

In [a] 0·01N-; [b] 0·50N-sodium hydroxide.

TABLE 5. *Hydrolysis of* 3-*substituted* 2-*thiohydantoins.*

Substituent	3-Methyl			3-Phenyl		3 : 5-Dimethyl	
[OH$^-$] (mole/l.)	0·001	0·010	0·001	0·002	0·010	0·001	0·010
$10^3 k_e$ (min.$^{-1}$)	3·0	5·5	5·3	6·8	10·7, 10·0	6·5	11·4
k_2 (l. mole^{-1} min^{-}.^{1})	60	60	106	102	118, 110	130	125

Equation (3) implies that 2-thiohydantoin should hydrolyse fairly rapidly even in very weakly alkaline solution; thus in changing the pH of the solution from 11·5 to 5·5 (*i.e.*, on reducing the hydroxide-ion concentration a million-fold), k_e should be reduced only a thousand-fold. In fact, even in distilled water (pH 5·5—6·0) hydrolysis occurred, as shown by the steady downward drift in pH of a 0·01M-solution (Table 3), with formation of thioureidoacetic acid (V; R = R′ = H). (A p$K_a' \approx 3{\cdot}6$ may be assumed for this acid, taking account of the pK_a' of hydantoic acid [11] and of the comparative inductive effects of the ureido- and the thioureido-group.[12]) The pH became constant at about 3·70, presumably because the acid-catalysed ring closure (V ⟶ I) became sufficiently rapid for equilibrium (I ⇌ V) to be established. The pK_a' given above being assumed, this pH requires a thioureidoacetic acid concentration of about 4×10^{-4}M, corresponding to 4% of hydrolysis; the drop in ultraviolet absorption at 259 mμ indicated 3% of hydrolysis. As expected, the absorption of a 5×10^{-5}M-solution at this wavelength showed a very much larger drop, about 65% hydrolysis being indicated after 156 hr. At the same time the wavelength of the peak shifted from 259 to 265 mμ. This may be due to some concurrent oxidation (to be discussed in a later paper).



A slow hydrolysis probably explains the gradual decrease (over a period of one week) in the intensity of colour given by a standard solution (6×10^{-5}M) of 5-*iso*butyl-2-thiohydantoin with the Folin–Denis reagent.[13] It appears desirable slightly to acidify standard solutions of 2-thiohydantoins to prevent this reaction.

[10] Cf. Simms, *J. Phys. Chem.*, 1928, **32**, 1121; 1929, **33**, 745.
[11] Zief and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2247.
[12] Kumler and Fohlen, *ibid.*, 1942, **64**, 1944.
[13] Folin and Denis, *J. Biol. Chem.*, 1912, **12**, 239; 1913, **14**, 95.

The thiohydantoin ring is stabilised by substitution at position 5 (Table 4).[14] 5 : 5-Dimethyl- and 5-*iso*propyl-2-thiohydantoin have pK_a' values of about 8·7;[1] this value has also been assumed for 5-methyl-2-thiohydantoin in calculating k_2 from k_c by equation (4). A pK_a' of 9·2 has been assumed for 1-phenyl-2-thiohydantoin, from analogy with the effect of substituting a phenyl group in thiourea.[1,15] 5 : 5-Diphenyl- and 5 : 5-pentamethylene-2-thiohydantoin were hydrolysed even more slowly than 5 : 5-dimethyl-2-thiohydantoin, little or no hydrolysis being observed in solutions in 0·01N-sodium hydroxide after several days.

3-Substituted 2-thiohydantoins (VI) are more weakly acidic (p$K_a' \approx 11$), ionising to give the anion (VII).[1] With these compounds also, hydrolysis seems to involve reaction of the hydroxide ion with the un-ionised fraction only, as shown by the rough constancy of the values of k_2 (Table 5) calculated from equation (3), $K_a' = 10^{-11}$ being assumed for all three compounds.

It is evident that substitution of 2-thiohydantoin alters its rate of hydrolyses both by the effect on the reactivity of the neutral molecule, and by the effect on the ionisation constant, and hence on the proportion of the compound available for hydrolysis at a given pH. The latter effect may be eliminated by comparing k_2 values. The reciprocals of the k_2 values for the variously substituted 2-thiohydantoins, relative to the value for the parent compound are as follows:

1-Methyl-3-phenyl	11	3 : 5-Dimethyl	44	3-Methyl	94
5-Methyl	18	1 : 3-Dimethyl	47	5 : 5-Dimethyl	2820
3-Ethyl-1-phenyl	23	3-Phenyl	52	5 : 5-Pentamethylene	>10,000
1-Phenyl	28	5-*iso*Propyl	51	5 : 5-Diphenyl	>10,000

Because of the experimental errors and the various approximations in the theoretical treatment, too much weight should not be attached to the precise numerical values given here. However, they indicate that, while substitution generally leads to decreased reactivity, the effect of geminal 5-groups is particularly strong,[14] probably because they oppose by non-bonded interactions the change from a trigonal (I) to a tetrahedral configuration (III) at $C_{(4)}$.[16] Substitution at $N_{(3)}$ slightly stabilises the neutral molecule, but this effect is outweighed by the less complete ionisation of these compounds and so the net effect is to accelerate hydrolysis.

From these results it seems that hydrolysis accounts for only a small part of the losses of 2-thiohydantoins in the Schlack and Kumpf procedure. Other possible degradative reactions will be discussed in subsequent papers.

Experimental

Materials [1] and general methods [1,9] have been described. Readings were taken with either a Unicam S.P. 500 or Beckman DU spectrophotometer. The cell compartment in the former instrument was cooled by running water, and no appreciable change in the temperature of a solution in the quartz cells was noted after 2—3 hr. In the Beckman instrument the temperature of the solution generally increased by 1—2° over such a period. Temperatures where not otherwise specified were in the range 17—23°. Rate constants were obtained by the usual graphical method.

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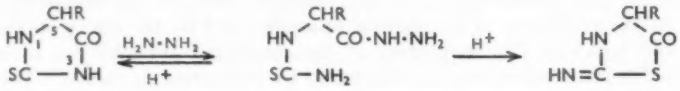
[14] Cf. Ingold, Sako, and Thorpe, *J.*, 1922, 1177.
[15] Walter, Ryan, and Lane, *J. Amer. Chem. Soc.*, 1956, **78**, 5560.
[16] Brown, Brewster, and Schechter, *ibid.*, 1954, **76**, 467.

1016. *Thiohydantoins. Part III.* Reactions with Amino-compounds.*

By J. T. Edward and S. Nielsen.

As model studies for a modification of Schlack and Kumpf's procedure,[1,2] we have investigated the deacylation of 1-acyl-2-thiohydantoins by aqueous hydrazine. 1-Benzoyl-2-thiohydantoin and 1-acetyl-5-methyl-2-thiohydantoin readily afforded benzhydrazide and acethydrazide respectively; however, instead of the expected 2-thiohydantoins (I; R = H and Me) the products proved to be the α-thioureido-hydrazides (II; R = H and Me).[3] The action of acid on the hydrazide (II; R = Me) afforded the thiohydantoin (I; R = Me) again, and a third compound which was probably 2-imino-4-methyl-5-thiazolinone (III; R = Me).[4]



(I) (II) (III)

The high yields of these hydrazides (II; R = H and Me) were probably a consequence of low solubility in water. The reaction of aqueous hydrazine with 2-thiohydantoin and with 5-methyl-, 3-phenyl-, 5-phenyl-, 5-benzyl-, and 5-*iso*propyl-2-thiohydantoin was shown by paper chromatography to be still incomplete after one week, and crystalline hydrazides could not be isolated from the last four reactions. On the other hand, reaction of 5-methyl-2-thiohydantoin with excess of benzylamine or phenylhydrazine was complete in 24 hours, but the products could not be obtained crystalline.

Experimental.—Thioureidoacethydrazide (II; R = H). A solution of 1-benzoyl-2-thiohydantoin (0·5 g.) in 50% aqueous hydrazine (5 ml.) began to deposit colourless prisms of *thioureidoacethydrazide* after 2 min.; after 30 min. the hydrazide (0·32 g.), m. p. 190° (decomp.) (Found: C, 24·0; H, 5·2. $C_3H_6ON_4S$ requires C, 24·3; H, 5·4%), was collected. It was soluble in concentrated mineral acids and alkalis, but had negligible solubility in common organic solvents except hot glacial acetic acid.

The filtrate from the hydrazide, overnight at 0°, deposited benzhydrazide, obtained after recrystallisation from methanol as plates, m. p. and mixed m. p. 112°. By ascending chromatography on Whatman No. 1 paper, with butanol saturated with water as the solvent system (solvent A), it had R_F 0·68; with propanol–water 7 : 3 (v/v) (solvent B), R_F = 0·86. Identical R_F values were shown by an authentic specimen. The zones of benzhydrazide were located by sprays of the Folin–Denis reagent [2,5] (blue spot) or of an acidic solution of *p*-dimethylaminobenzaldehyde (yellow spot).

α-Thioureidopropionhydrazide (II; R = Me). The hydrazide began to be deposited within 20 min. of mixing from a solution of 1-acetyl-5-methyl-2-thiohydantoin (2·0 g.) in 50% aqueous hydrazine (10 ml.). After 12 hr. the *hydrazide* (1·9 g.) was collected: it had m. p. 182° (Found: C, 29·2; H, 6·2; S, 19·7. $C_4H_{10}ON_4S$ requires C, 29·6; H, 6·2; S, 19·7%). The filtrate on evaporation afforded acethydrazide, identified by m. p., mixed m. p., and chromatographic comparison with an authentic specimen (R_F 0·29 in solvent A, 0·53 in solvent B).

α-Thioureidopropionhydrazide was also formed by the action of hydrazine on 5-methyl-2-thiohydantoin. Its solubility behaviour was similar to that of thioureidoacethydrazide. With benzaldehyde in aqueous acid it gave pale yellow plates of *benzaldehyde α-thioureidopropionylhydrazone*, m. p. 201 (Found: C, 51·8; H, 5·5. $C_{11}H_{14}ON_4S$ requires C, 51·8; H, 5·6%).

* Part II, preceding paper.

[1] Schlack and Kumpf, *Z. physiol. Chem.*, 1926, **154**, 125; Waley and Watson, *J.*, 1951, 2394.
[2] Edward and Nielsen, *Chem. and Ind.*, 1953, 197.
[3] Cf. Fosse, Hagene, and Du Bois, *Compt. rend.*, 1924, **178**, 578.
[4] Edman, *Acta Chem. Scand.*, 1956, **10**, 761.
[5] Folin and Denis, *J. Biol. Chem.*, 1912, **12**, 239; 1913, **14**, 95.

The hydrazide (10 mg.) was dissolved in 5N-hydrochloric acid (2 ml.). After 2 hr., paper chromatography of the solution with solvent A and the Folin–Denis spray showed the presence of 5-methyl-2-thiohydantoin (R_F 0·69), and of traces of the hydrazide (R_F 0·21) and of a third compound (III?) (R_F 0·50).

Chromatographic examination of the reaction between hydrazine and 2-thiohydantoins. Solutions of 2-thiohydantoin and of 3-phenyl-, 5-phenyl-, 5-methyl-, 5-*iso*propyl-, and 5-benzyl-2-thiohydantoin (0·2 g.) in 50% aqueous hydrazine (2 ml.), after storage for one week, were evaporated to dryness. The residues were taken up in water and examined by ascending chromatography with solvent A. In all cases the Folin–Denis spray showed two zones, the first due to the original 2-thiohydantoin; the second zone also reacted with *p*-dimethylaminobenzaldehyde, and so was a thioureidohydrazide (II). R_F values were as follows:

Substituent	—	3-Ph	5-Ph	5-Me	5-Pr^i	5-CH_2Ph
2-Thiohydantoin	0·45	0·75	0·75	0·69	0·90	0·90
Thioureidohydrazide	0·10	0·19	0·19	0·22	0·40	0·45

Reaction of 5-methyl-2-thiohydantoin with benzylamine and phenylhydrazine. The thiohydantoin (0·5 g.) was dissolved in benzylamine (3 ml.) and in phenylhydrazine (3 ml.). After 24 hr. the excess of base was removed at reduced pressure. The residual syrups could not be crystallised; paper chromatographic examination with solvent A showed a compound, R_F 0·82, from benzylamine and another compound, R_F 0·75, from phenylhydrazine, and the absence of 5-methyl-2-thiohydantoin in both cases.

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1017. *Analogues of Aminacrine and Rivanol Derived from 1 : 10-Diaza-anthracene.*

By D. M. Besly and A. A. Goldberg.

5-Aminoacridine (aminacrine) and 5 : 8-diamino-3-ethoxyacridine (rivanol) are valuable antibacterial agents for application to wounds. It was of interest to prepare analogues containing the 1 : 10-diaza-anthracene nucleus in order to determine whether the extra ring-nitrogen atom increased solubility and antibacterial activity.

2-Chloro-4-nitrobenzoic acid with 5-amino-2-methoxypyridine gave 2-(2-methoxy-5-pyridylamino)-4-nitrobenzoic acid. Cyclisation by the Magidson–Grigorovski method yielded 9-chloro-2-methoxy-6-nitro-1 : 10-diaza-anthracene which was converted by ammonia in phenol into the 9-amino-6-nitro-compound. Reduction with iron then gave the required 6 : 9-diamine.

9-Amino-2-methoxy-1 : 10-diaza-anthracene was obtained from *o*-chlorobenzoic acid and 5-amino-2-methoxypyridine by the same route. Attempts to prepare 9-amino-1 : 10-diaza-anthracene were not successful because of the failure of the unsubstituted 2-3′-pyridylaminobenzoic acids [1] to undergo cyclisation.

Experimental.—*2-(2-Methoxy-5-pyridylamino)benzoic acid.* A mixture of *o*-chlorobenzoic acid (15·6 g., 0·1 mol.), anhydrous potassium carbonate (14 g., 0·1 mol.), 5-amino-2-methoxypyridine (9 g., 0·075 mol.), and a trace of copper bronze–cuprous iodide catalyst was stirred at the b. p. with pentyl alcohol (100 c.c.) for 3 hr.; water was separated by a Dean and Stark apparatus. The alcohol was removed in a current of steam, the residual solution filtered (charcoal) and adjusted with 5N-hydrochloric acid to pH 4, and the precipitate collected. Crystallisation from boiling aqueous ethanol gave the *acid* (8 g., 48%) in grey needles, m. p. 162—165° [Found: *M* (by titration), 242; N, 11·6%. $C_{13}H_{12}O_3N_2$ requires *M*, 244; N, 11·5%].

[1] Besly and Goldberg, *J.*, 1954, 2448.

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9-*Chloro*-2-*methoxy*-1 : 10-*diazanthracene*. The foregoing acid (12 g.) was refluxed with phosphoryl chloride (72 c.c.) for 6 hr., the excess of reagent distilled off, and the residual oil poured on crushed ice (900 g.) and aqueous ammonia (300 c.c.; *d* 0·88). After being kept overnight at 0° the greenish-yellow precipitate was collected (12 g.; m. p. 130°), washed with water, and dried at 15°/10 mm. (KOH). The *chloro*-compound crystallised from ligroin (b. p. 80—100°) in pale yellow needles, m. p. 140° (Found: N, 11·3; Cl, 15·7. $C_{13}H_9ON_2Cl$ requires N, 11·5; Cl, 14·6%).

9-*Amino*-2-*methoxy*-1 : 10-*diaza-anthracene hydrochloride*. The foregoing compound (5·5 g.) was heated with dry phenol (30 g.) for 1 hr. at 110° and then ammonium carbonate (10 g.) added as rapidly (*ca.* ½ hr.) as frothing would permit. After a further hour at 110°, the cooled mixture was poured into anhydrous ether (250 c.c.). The yellow precipitate (4·5 g.; m. p. 270°), on crystallisation from 0·1N-hydrochloric acid (9 c.c./1 g.) and then dilute aqueous ammonium chloride, gave the pure *hydrochloride* in pale yellow needles, m. p. 288° (Found: equiv., 261; N, 16·3; Cl, 15·4%. $C_{13}H_{12}ON_3Cl$ requires equiv., 261·5; N, 16·1; Cl, 13·6%).

2-(2-*Methoxy*-5-*pyridylamino*)-4-*nitrobenzoic acid*. 2-Chloro-4-nitrobenzoic acid (54 g.), potassium carbonate (38 g.), copper bronze (0·5 g.), cupric oxide (0·5 g.), and 5-amino-2-methoxypyridine (27 g.) were stirred with pentyl alcohol (300 c.c.) at the b. p. for 6 hr. Treatment as described above then gave the *acid* (49 g., 78%) as an orange powder which crystallised from acetic acid (50 c.c./g.), as orange needles, m. p. 250° [Found: *M* (by titration), 284; N, 14·7%. $C_{13}H_{11}O_5N_3$ requires *M*, 289; N, 14·5%].

9-*Chloro*-2-*methoxy*-6-*nitro*-1 : 10-*diaza-anthracene*. The foregoing acid (10 g.) was cyclised by refluxing with phosphoryl chloride (80 c.c.) for 6 hr. and the mixture treated as above. The product (9·5 g.) had m. p. 210—214°; the pure *compound* separated from carbon tetrachloride in pale yellow needles, m. p. 218—220° (Found: N, 14·5; Cl, 12·4. $C_{13}H_8O_3N_3Cl$ requires N, 14·5; Cl, 12·2%).

9-*Amino*-2-*methoxy*-6-*nitro*-1 : 10-*diaza-anthracene*. The foregoing compound (21 g.) was heated with dried phenol (150 g.) at 110° for 1 hr. and then powdered ammonium carbonate (50 g.) was added with occasional stirring during 1 hr. After a further hour at 110° the mixture was poured into excess of anhydrous ether, and the crude product (13·6 g.; m. p. 285°) collected. The pure *hydrochloride monohydrate* separated from dioxan–water–acetone in orange needles, m. p. 300° (Found: N, 17·3; Cl, 10·8. $C_{13}H_{11}O_3N_4Cl,H_2O$ requires N, 17·2; Cl, 10·9%).

6 : 9-*Diamino*-2-*methoxy*-1 : 10-*diaza-anthracene hydrochloride*. A solution of stannous chloride dihydrate (30 g.) in 10N-hydrochloric acid (30 c.c.) was added portionwise to a suspension of the foregoing nitro-compound (5 g.) in acetic acid (60 c.c.) stirred at 50°. The nitro-compound dissolved with evolution of heat and a crystalline precipitate was rapidly formed. After ½ hour's stirring the mixture was chilled, then filtered on sintered glass, and the solid stirred with ice and 5N-sodium hydroxide. The diamine was collected and dissolved in methanol (100 c.c.) containing a slight excess of hydrochloric acid, and hydrogen sulphide passed in. The filtered (charcoal) solution was diluted with boiling water to incipient precipitation and chilled: the *hydrochloride* separated as an orange powder, m. p. 296° (Found: N, 19·8; Cl, 13·0. $C_{13}H_{13}ON_4Cl$ requires N, 20·2; Cl, 12·8%).

Antibacterial activitites. The bacteriostatic activities against a series of Gram-negative and Gram-positive organisms are shown in the Table as the dilution potential (pD) which completely inhibits growth of the organism (inoculum 2 × 10^6 organisms/10 c.c. of medium) in Lab-Lemco broth incubated at 37° for 48 hr. (pD *x* means a dilution of 1 part compound in 10^x parts broth.

Organism	Compound * I	II	III	IV
Staphytococcus pyogenes aureus	5·1	4·6	4·9	4·8
Streptococcus haemolyticus (Aronson)	5·1	5·2	5·5	5·7
Bacillus coli	4·8	4·9	4·6	5·5
Bacillus proteus	4·8	4·0	4·0	3·0
Pseudomonas pyocyaneous	3·3	3·3	4·6	3·0
Bacillus subtilis	5·1	4·9	5·2	4·8

* I, 5-Aminoacridine hydrochloride (aminacrine); II, 9-amino-2-methoxy-1 : 10-diaza-anthracene hydrochloride; III, 5 : 8-diamino-3-ethoxyacridine hydrochloride (rivanol); IV, 6 : 9-diamino-2-methoxy-1 : 10-diaza-anthracene hydrochloride.

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1018. *Preparation of Carbonyl Compounds by Use of Dinitrogen Tetroxide. Part II.*[1] *Alkyl Aryl Ketones.*

By J. Grundy.

Field and Grundy [1] oxidised benzyl alcohols with dinitrogen tetroxide to prepare aromatic aldehydes; application of this reagent to the preparation of aryl alkyl ketones is now reported. In combination with the aldehyde preparation,[1] the method is useful for introducing an acyl in place of a carboxyl group: $R{\cdot}CO_2H \longrightarrow R{\cdot}CH_2{\cdot}OH \longrightarrow R{\cdot}CHO \longrightarrow R{\cdot}CHR'{\cdot}OH \longrightarrow R{\cdot}COR'$. The acyl group introduced is unambiguously oriented, and the method can be applied to, *e.g.*, *o*-halogenoaryl alkyl ketones.

Interaction of organocadmium compounds and acid chlorides [2] provides a valuable conversion of a carboxylic acid into a ketone; the use of dinitrogen tetroxide is, however, a still simpler technique and even in the four-stage process from the acid will give comparable yields.

The intermediate carbinols were usually obtained from the appropriate aromatic aldehyde and Grignard reagent, an excess of the latter preventing contamination of the carbinol with starting aldehyde. With methoxy-aldehydes some dealkylation occurred.

Reaction of the carbinols and dinitrogen tetroxide in chloroform followed the course previously described. Steric retardation of the reaction rate was observed with *o*-substituted 1-phenylethanols. Production of tars on distillation of reaction mixtures even at reduced pressures and liberation of dinitrogen tetroxide suggested formation of intermediates. However, residual intermediate was decomposed smoothly when the reaction mixture was heated on the water-bath or steam-distilled; the latter was the best method of isolating the ketones. The yields of ketones obtained are given in Table 1.

Table 1.

Ketone	Yield (%)	Ketone	Yield (%)	Ketone	Yield (%)
Acetophenone	98	*o*-Chloroacetophenone	95	*o*-Methoxyacetophenone	90
Propiophenone	98	*m*-Chloroacetophenone	90	*p*-Methoxyacetophenone	90
Butyrophenone	98	*p*-Chloroacetophenone	92	*m*-Methylacetophenone	94
Valerophenone	96	*o*-Bromoacetophenone	93	*p*-Methylacetophenone	95
Octyl phenyl ketone	92	*m*-Bromoacetophenone	91	*p*-Nitroacetophenone ...	88
		p-Bromoacetophenone	92	Benzophenone	89

Experimental.—Dinitrogen tetroxide. This was prepared as indicated previously [1] and the same concentration used.

Preparation of carbinols. The Grignard reagent was prepared in ether in the usual way from the alkyl iodide; the expected yields were based on the results of Gilman *et al.*[3] The aldehyde (0·6 mol.) in ether was added, and the cooled mixture decomposed by aqueous ammonium chloride. The carbinols were isolated in the usual way, yields being given in Table 2.

Table 2. *Yields of carbinols* $R{\cdot}C_6H_4{\cdot}CHR'{\cdot}OH$.

R	R′	B. p./mm.	Yield (%)	R	R′	B. p./mm.	Yield (%)	R	R′	B. p./mm.	Yield (%)
o-Cl	Me	80°/2	74	*m*-Br	Me	98°/2·5	78	*m*-Me	Me	100/4	76
m-Cl	Me	98/4·5	92	*p*-Br	Me	94/2	56	*p*-Me	Me	102/8	68
p-Cl	Me	90/2·5	70	*o*-MeO	Me	99/3·5	56	H	n-C_8H_{17}	130—134/2·5	60
o-Br	Me	100/3·5	85	*p*-MeO	Me	104/3	62				

1-p-*Nitrophenylethanol.* This was prepared as described by Ford-Moore and Rydon.[4]

Preparation of ketones. A solution of the carbinol (0·05—0·1 mole) in dry chloroform (3 vol.) was cooled in an ice-bath and a slight excess of the dinitrogen tetroxide solution added.

[1] *J.*, 1955, 1110, is considered to be Part I.
[2] Shirley, "Organic Reactions," Vol. 8, p. 28.
[3] Gilman, Zoellner, and Dickey, *J. Amer. Chem. Soc.*, 1929, **51**, 1579; Gilman and McCracken, *ibid.*, 1923, **45**, 2462.
[4] Ford-Moore and Rydon, *J.*, 1946, 679.

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The mixture was kept in the bath for 1 hr., then at room temperature for about 6 hr. or overnight in the refrigerator. Finally it was washed with the calculated amount of sodium carbonate solution (10%) and then with water. Solvent was removed (water-bath), heating being continued until oxides of nitrogen were no longer evolved. Steam-distillation or distillation at reduced pressure then gave the ketone.

Identification of ketones. The ketones were characterised as the following 2 : 4-dinitrophenylhydrazones, prepared according to Brady's method [5] and recrystallised from xylene: acetophenone, m. p. and mixed m. p. 247—248°; propiophenone, m. p. 192—193° (Vogel [6] gives m. p. 191°); butyrophenone, m. p. 194—195° (Vogel [6] gives m. p. 190°); valerophenone, m. p. 165—166° (Vogel [6] gives m. p. 166°); ***n-octyl phenyl ketone***, m. p. 238—239° (Found: N, 14·1. $C_{21}H_{26}O_4N_4$ requires N, 14·0%); benzophenone, m. p. 242—243 (lit.,[6,7] m. p. 238°, 240—241°); *o*-chloroacetophenone, m. p. 204—205° (lit.,[8] m. p. 206°); m-***chloroacetophenone***, m. p. 207—208° (Found: N, 16·6. $C_{14}H_{11}O_4N_4Cl$ requires N, 16·7%); *p*-chloroacetophenone, m. p. 240—241° (Vogel [6] gives m. p. 239°); *o*-bromoacetophenone, m. p. 186—187 (lit.,[9] m. p. 187°); m-***bromoacetophenone***, m. p. 225—226° (Found: N, 14·7. $C_{14}H_{11}O_4N_4Br$ requires N, 14·7%); *p*-bromoacetophenone, m. p. 232—233° (Vogel [6] gives m. p. 230°); *o*-methoxyacetophenone, m. p. 191—192° (lit.,[10,11] m. p. 185°, 196—198°); *p*-methoxyacetophenone, m. p. 225—226° (lit.,[6,11] 220°, 233—234°); *m*-methylacetophenone, m. p. 207—208° (Vogel [6] gives m. p. 207°); *p*-methylacetophenone, m. p. 256—257° (Vogel [6] gives m. p. 258°); and p-***nitroacetophenone***, m. p. 268—269° (Found: N, 20·1. $C_{14}H_{11}O_6N_5$ requires N, 20·3%).

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[5] Brady, *J.*, 1931, 757.
[6] Vogel, "Practical Organic Chemistry," Longmans Green, London, 1948.
[7] Roberts and Green, *J. Amer. Chem. Soc.*, 1946, **68**, 214.
[8] Borsche and Scriba, *Annalen*, 1939, **541**, 283.
[9] Borsche and Herbert, *ibid.*, 1941, **546**, 297.
[10] Pinder and Smith, *J.*, 1954, 113.
[11] Borsche and Barthenheier, *Annalen*, 1942, **553**, 250.

1019. *The Mechanism of the Vapour-phase Bromination of Naphthalene.*

By E. A. HALEVI, ISRAEL LOEFF, and GABRIEL STEIN.

IN Wibaut, Sixma, and Suyver's experiments [1] bromine and naphthalene were passed, in nitrogen, over glass wool or pumice at 250—600°. The percentage of β-bromonaphthalene in the monobromonaphthalene fraction rises from a low value at 250° along a sigmoid curve, which has maximum slope at 450—480°, and then approaches 50% asymptotically (curve through □ in the Figure). They concluded that bromination occurs *via* two competing mechanisms, each predominant in a different range: (i) at low temperatures, an electrophilic reaction at the packing surface favouring α-substitution, and (ii) at high temperatures, abstraction of hydrogen atoms by atomic bromine to form naphthyl radicals, which then react with molecular bromine. The first step was assumed to have a very low activation energy, and to be unselective with regard to production of α- and β-naphthyl radicals.

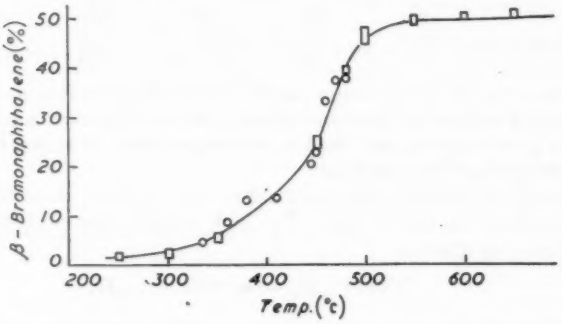
There appears to be no direct proof for these mechanisms. Korvezee and Scheffer [2] showed that any two competing reactions, both of first order with respect to bromine, could be made to yield a theoretical curve in equally good agreement with experiment. The large number of virtually freely adjustable parameters available seem to make even this restriction of kinetic order unnecessarily stringent. Moreover, the experiments involved packed vessels, so that there is no experimental evidence that the low-temperature

[1] (*a*) Suyver and Wibaut, *Rec. Trav. chim.*, 1945, **64**, 65; (*b*) Wibaut, Sixma, and Suyver, *ibid.*, 1949, **68**, 525; (*c*) Sixma, *ibid.*, p. 915; (*d*) Sixma and Wibaut, *ibid.*, 1950, **69**, 577.
[2] Korvezee and Scheffer, *ibid.*, p. 497.

reaction is heterogeneous. They concluded that it must be so from analogy with electrophilic liquid-phase bromination and the assumption that a heterolytic reaction in the vapour phase must involve either a three-body collision or, more plausibly, a surface reaction.

We have determined the product ratio under conditions different from those of ref. 1, using (*a*) a static system, (*b*) an unpacked vessel, and (*c*) no diluent gas.

(*a*) *Thermal Bromination.*—Approximately equimolar quantities of bromine and naphthalene (the latter in slight excess) were mixed in an evacuated vessel, preheated to the required temperature. After reaction the products were condensed, and the monobromonaphthalene fraction was distilled off *in vacuo*, the β/α ratio being determined in it spectrophotometrically (Figure, O).



Up to 480° our results duplicate Wibaut, Sixma, and Suyver's [1] quite well. Above 480° our results (not shown) became erratic, the percentage of β-bromonaphthalene being abnormally low, usually 20—30%.

(*b*) *Surface Effect.*—Although our method was unsuitable much above 480°, it appeared that surface effects could still be responsible for the erratic results there. Brominations were carried out in presence of Pyrex wool. Even at relatively low temperatures, increase of surface-to-volume ratio raised the yield of β-bromonaphthalene well above the value obtained in unpacked vessels, as follows: at 360°, 20·3%; at 370°, 22·4%. Therefore some surface reaction must occur, but the results are incompatible with the assumption [1] of a surface reaction's favouring α-bromination.

We tried to eliminate surface effects by " curing " the reaction vessels by coating them with carbon according to Maccoll and Thomas's method.[3] In " cured " vessels, our results agreed with those of ref. 1 at higher temperatures, within our large experimental error, so that by avoiding surface effects, and thus presumably obtaining homogeneous reactions, we could duplicate the findings of the previous workers over our entire working range.

Experiments were also done to determine whether α- and β-bromonaphthalene isomerise on glass in our conditions, as they do under the influence of ferric salts [1b] or silica gel,[4] by treating β-bromonaphthalene under various conditions. Isomerisation was much too slow to account for our erratic results in " uncured " vessels at high temperatures, at which bromination is virtually instantaneous. Moreover, synthetic mixtures of the approximate product composition did not equilibrate appreciably.

(*c*) *Photochemical Bromination.*—We confirmed that there are two competing mechanisms of bromination of naphthalene, but our duplication of the results of ref. 1 under such very different conditions showed that neither is heterogeneous. Wibaut, Sixma, and

[3] Maccoll and Thomas, *J.*, 1955, 980.
[4] Mayer and Schiffner, *Ber.*, 1934, **67**, 67.

Suyver's high-temperature mechanism, while still unproved, appears plausible. Their low-temperature mechanism, however, is untenable. Instead, direct attack of atomic bromine on carbon, with synchronous or subsequent elimination of a hydrogen atom, can be postulated. The higher free valence of the α-position [5] would lead to preferential substitution there. A crude calculation confirms that the equilibrium concentration of bromine atoms is probably high enough, even at lower temperatures, to account for the rate of bromination.

To determine whether the low-temperature brominations required atomic bromine, we did brominations under illumination. If both mechanisms were due to atomic bromine, the isomer ratio would not be altered. The experiments were qualitative, the unmodified reaction vessel being illuminated by two 500 w projection lamps. The results (% of β-isomer) are shown in the Table.

	300°	320°	350°	380°	400°	420°
Thermal (from Figure, curve)	2·5	3·4	5·5	8·5	11·2	15·0
Light	1·3	7·6	8·3, 7·9	13·9	26·1	27·2, 22·7

Above 350° the proportion of β-bromonaphthalene clearly increases. Thus increase of the standing concentration of bromine atoms photochemically accelerates the non-selective reaction preferentially, and does so at temperatures at which this mechanism is significant even under thermal conditions.

We conclude that two *homogeneous* mechanisms are involved, only the one favouring a high β/α ratio requiring bromine atoms. The high-temperature mechanism of ref. 1, the rate-determining step of which is

$$Br\cdot + C_{10}H_8 \longrightarrow HBr + C_{10}H_7\cdot \quad . \quad . \quad . \quad . \quad . \quad (1)$$

appears reasonable. However their assumption [1] that the activation energy of this step is 0—5 kcal./mole does not seem justified. As the dissociation energy of the C–H bond in naphthalene should be close to that in benzene (106 kcal./mole [6]), the dissociation energy of H–Br is approximately 86 kcal./mole, and as the reverse reaction of (1) should require [7] 0—2 kcal./mole, the activation energy of reaction (1) should be about 20 kcal./mole. The lack of selectivity of reaction by this mechanism would arise even if the rate-determining step were activated, provided the strengths of the C–H bonds in the α- and the β-position are the same.

A reasonable interpretation of the low-temperature mechanism involves the reaction of a bromine molecule with naphthalene. Bergmann [10] has suggested an addition–elimination sequence. One *a priori* objection is that these reactions are generally presumed to be heterolytic and therefore not characteristic homogeneous gas-phase reactions. However, Maccoll and Thomas's [8] pyrolyses of alkyl bromides, showing that homogeneous elimination of HBr can take place and partakes of considerable heterolytic character, disfavour this argument against the molecular elimination mechanism.

That illumination increases the percentage of β-isomer appreciably only at the higher temperatures suggests that the small but increasing percentage of β-isomer produced thermally at low temperatures arises from the " molecular " mechanism, as postulated by the previous workers,[1,2] who suggest a difference of 3—4 kcal./mole between reaction at the α- and the β-position.

Experimental.—Materials. α-Bromonaphthalene was prepared from α-naphthylamine by the Sandmeyer reaction and repeatedly fractionally distilled under reduced pressure. The β-isomer was similarly prepared by van der Kam's method,[9] twice steam-distilled from an

[5] Coulson, " Valence," Oxford Univ. Press, 1952, p. 255.
[6] Landolt–Börnstein, " Tabellen," Atom und Molekular Physik, Band I, 2 Teil, Molekeln I, 1951.
[7] Szwarc, *Chem. Rev.*, 1950, **47**, 81.
[8] Maccoll and Thomas, *Nature*, 1955, **176**, 392.
[9] van der Kam, *Rec. Trav. chim.*, 1926, **45**, 569.
[10] Bergmann, personal communication.

alkaline medium, and recrystallised (alcohol). Naphthalene was from B.D.H. (" for Molecular-weight Determination "). *n*-Hexane (Philips Petroleum Co., U.S.A.), stated to contain more than 99% of *n*-hexane, was redistilled several times.

Method. The reaction vessel was a Pyrex glass tube, 28 mm. in diameter and 30—35 cm. long (vol. *ca.* 200 c.c.). A side arm, connected to a vacuum system, contained a bromine ampoule with a magnetic breaker. Where a " cured " vessel was required, its interior surface was carbonised [3] by pyrolysis of alkyl bromide in the evacuated vessel at about 400°.

An ampoule containing naphthalene was sealed to the bottom of the vessel; 1·5—2 mmoles of naphthalene and bromine were used, the former being in slight excess. The whole vessel was evacuated to 10^{-3}—10^{-4} mm., sealed off, and put into the preheated oven, the naphthalene in the sealed-on ampoule being kept in liquid nitrogen. The bromine ampoule was broken and the naphthalene allowed to warm, so that the bromine and naphthalene distilled into the reaction vessel. The reaction was practically instantaneous at the higher temperatures and took 30—60 min. at the lowest temperatures. As the reaction reached completion, the products were condensed in the original naphthalene ampoule.

The photochemical experiments were performed in the same Pyrex apparatus. Unfiltered illumination from two 500 w projection lamps was employed so that only wavelengths above 3000 Å were effective.

Analysis. The products were transferred with diethyl ether to a small distillation flask and the ether was removed under reduced pressure. Excess of naphthalene was sublimed off at 80°/7 mm. on a cold finger containing solid carbon dioxide–ethanol. The monobromides were then distilled at about 130°/<7 mm. the b. p.s of the dibromides being considerably higher at this pressure. Ultraviolet absorption spectra of the two monobromides in *n*-hexane were measured with a Beckman Model D.U. spectrophotometer.

Because of the similarity of the absorption curves of the monobromonaphthalenes, we measured the optical densities of mixtures at 10 wavelengths between 2600 and 2950 Å, and reduced the results to two simultaneous equations by the method of least squares.

Spectrophotometric analysis were generally reliable to about ±2% of β-bromonaphthalene.

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1020. *Tetra-aquopalladium*(II) *Perchlorate.*

By STANLEY E. LIVINGSTONE.

PALLADIUM perchlorate, previously known only in aqueous perchloric acid solution,[1,2] has now been isolated as a crystalline tetrahydrate which deliquesces in moist air. The water of crystallisation is not removed *in vacuo* (P_2O_5) and so the solid probably contains the square planar ion $[Pd(H_2O)_4]^{2+}$, hitherto unknown in a simple salt.

The absorption spectrum in 1M-perchloric acid shows a maximum at 382 mμ (ε 200) a minimum at 310 mμ (ε 60). The aqueous solution of the compound darkens at first, but equilibrium is reached after some hours at room temperature; the conductance and absorption spectrum [$\lambda_{max.}$ 268 mμ (ε 4800)] remain unaltered after 7 days. The values of the molecular conductivity (Λ) in water at 25° are:

v (l.)	20	100	1000
Λ (mhos)	611	710	788

The pH of a 10^{-2}M-solution is 1·8, and at 10^{-3}M, 2·8. The addition of sodium perchlorate and subsequent boiling precipitates hydrated palladium(II) oxide. The brown aqueous solution is therefore a collodial suspension of hydrated palladium(II) oxide.

The hydrated palladium(II) ion is stable in solution only at low pH and in the absence of any ligand capable of co-ordinating to palladium. These conditions are fulfilled in

[1] Templeton, Watt, and Garner, *J. Amer. Chem. Soc.*, 1943, **65**, 1608.
[2] Sundaram and Sandell, *ibid.*, 1955, **77**, 855.

perchloric acid solutions at concentrations greater than 0·1M with respect to perchloric acid.

Experimental.—Tetra-aquopalladium(II) *perchlorate.* Palladium sponge was dissolved in concentrated nitric acid, perchloric acid (72%) added, and the solution heated till it fumed strongly; on cooling, it deposited brown needles of the *perchlorate.* These were washed with perchloric acid, pressed between filter papers, and dried *in vacuo* (over NaOH then P_2O_5) (Found: Cl, 18·9; Pd, 27·9. $H_8O_{12}Cl_2Pd$ requires Cl, 18·8; Pd, 28·2%).

Spectra. The absorption spectra were obtained on a Unicam S.P. 500 spectrophotometer, I cm. quartz cells being used.

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1021. *Simple Preparation of* N^1-*Substituted* N^4N^4-*Phthaloyl-, -Succinoyl-, and -Adipoyl-sulphanilamides.*

By M. Z. BARAKAT, S. K. SHEHAB, and M. M. EL-SADR.

PREVIOUSLY it was reported that sulphapyridine with succinic and phthalic anhydrides at <100° gives acid amides $HO_2C{\cdot}X{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY$ but at >100° gives the imides $X(CO)_2N{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY$. With maleic anhydride the acid amide is the sole product, even at 190°. None of the diamides (I) is obtained in condensations with an-

(I) $X(CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NHY)_2$

hydrides.[1,2] Other methods have been reported for the preparation of *p*-succinimidobenzenesulphonamide[3] and (*p*-phthalimidobenzenesulphonamido)pyridine.[4] We now report a general and simple method for preparing the imides: it consists of fusing succinic or phthalic acid with a sulphonamide at 200° for 30 minutes. It is analogous to the recent preparation of *N*-arylphthalimides.[5] Fusing adipic acid with sulphanilamide or certain derivatives yields the corresponding diamides (I).

We have thus prepared several known N^4N^4-succinimido- and -phthalimido-derivatives of sulphanilamides, as well as some new imides for chemotherapeutic testing.

Experimental.—The imides and diamides melted with decomposition, gave positive sodium fusion tests for nitrogen and sulphur, and negative diazotisation and acidity tests, and did not produce a colour with 10% alcoholic potassium hydroxide (cf. ref. 5).

Succinic acid (1·18 g., 0·01 mole) or phthalic acid (1·66 g., 0·01 mole) was heated with sulphanilamide (1·72 g., 0·01 mole), or an analogue thereof, at 200° for 30 min., protected by a calcium chloride tube. The product was allowed to cool, powdered, and recrystallised from the appropriate solvent. The compounds tabulated were prepared. Solvents of crystallisations have been reported for similar compounds.[1,7]

Similarly new N^4N^4-*succinimido-derivatives* were prepared from: sulphadiazine (yield 0·8 g.), m. p. 282° (from acetic acid) (Found: C, 49·4; H, 4·0; N, 14·0; S, 8·5. $C_{14}H_{12}O_4N_4S,C_2H_4O_2$ requires C, 49·0; H, 4·1; N, 14·3; S, 8·2%); sulphaguanidine (2·5 g.), m. p. 248—250° (from water) (Found: C, 42·3; H, 4·4; N, 17·6; S, 10·45. $C_{11}H_{12}O_4N_4S,H_2O$ requires C, 42·0; H, 4·5; N, 17·8; S, 10·2%); sulphamerazine (1·6 g.), m. p. 288—290° (from alcohol) (Found: C, 51·9; H, 4·3; N, 15·8; S, 9·1. $C_{15}H_{14}O_4N_4S$ requires C, 52·0; H 4·05; N, 16·2; S, 9·25%);

[1] Shapiro and Bergmann, *J. Org. Chem.*, 1941, **6**, 774.
[2] Miller, Rock, and Moore, *J. Amer. Chem. Soc.*, 1939, **61**, 1198; Moore and Miller, *ibid.*, 1942, **64**, 1572.
[3] Reid, Reynolds, and Seymour, Herts Pharmaceuticals Ltd., B.P. 595,039/1947; Mayer, *Österr. Chem. Ztg.*, 1951, **52**, 32.
[4] Horii and Yamada, Jap. Patent, 1948, 176,169; *Chem. Abs.*, 1951, **45**, 7145.
[5] Barakat, Shehab, and El-Sadr, *J.*, 1957, 4133.
[6] Picard, Reid, Reynolds, and Seymour, *J.*, 1948, 821.
[7] Vonesch and Velasco, *Arch. Farm. Bioquím. Tucumán*, 1944, I, 241; *Chem. Abs.*, 1945, **39**, 251.

Parent sulpha-compound	Cryst. from	M. p.	Formula	N (%) Found	N (%) Calc.	Yield (%)
N⁴N⁴-Succinoyl derivatives.						
Sulphanilamide ...	AcOH	285° [a]	$C_{10}H_{10}O_4N_2S$	11·3	11·0	55
Sulphathiazole	EtOH	274—275 [b]	$C_{13}H_{11}O_4N_3S_2,C_2H_5{\cdot}OH$	11·2	11·0	52
N⁴N⁴-Phthaloyl derivatives.						
Sulphanilamide ...	C_5H_5N	334—335 [c]	$C_{14}H_{10}O_4N_2S,C_5H_5N$	10·8	11·0	40
Sulphathiazole	AcOH	274—276 [d]	$C_{17}H_{11}O_4N_3S_2$	11·3	10·9	52
Sulphapyridine ...	AcOH	281 [e]	$C_{19}H_{13}O_4N_3S,C_2H_4O_2$	9·65	9·6	48

[a] Lit., 282—283°, 288—289°, 290—290·5°. [b] Lit., 266—267°, 269—270°. [c] Lit., 334°, 320—322°. [d] Lit., 269—269·5°. [e] Lit., 277°, 279—281°, 278—278·5°.

sulphamethazine (1·5 g.), m. p. 256° (from alcohol) (Found: C, 53·1; H, 4·8; N, 15·5; S, 9·45. $C_{16}H_{16}O_4N_4S$ requires C, 53·3; H, 4·4; N, 15·6; S, 8·9%).

The following new N⁴N⁴-*phthalimido-derivatives* were similarly prepared from: sulphadiazine (2 g.), m. p. 318—320° (from pyridine and water) (Found: C, 56·6; H, 3·3; N, 15·1; S, 8·5. $C_{18}H_{12}O_4N_4S$ requires C, 56·8; H, 3·2; N, 14·7; S, 8·4%); sulphamerazine (2·2 g.), m. p. 294—296° (from pyridine and water) (Found: C, 58·2; H, 3·7; N, 14·0; S, 8·05. $C_{19}H_{14}O_4N_4S$ requires C, 57·9; H, 3·55; N, 14·2; S, 8·1%); sulphamethazine (1·8 g.), m. p. 220—222° (from acetic acid) (Found: C, 56·3; H, 4·3; N, 11·8; S, 6·9. $C_{20}H_{16}O_4N_4S,C_2H_4O_2$ requires C, 56·4; H, 4·3; N, 12·0; S, 6·8%).

With adipic acid, under identical conditions, *diamides* (I) were obtained from: sulphanilamide, m. p. 302° (lit.,[a] 287°) (Found: C, 47·2; H, 4·95; N, 11·8; S, 14·0. Calc. for $C_{18}H_{22}O_6N_4S_2$: C, 47·6; H, 4·85; N, 12·3; S, 14·1%); sulphadiazine (0·4 g.), orange (from acetic acid), m. p. 234° (Found: C, 50·6; H, 4·6; N, 16·4; S, 9·4. $C_{26}H_{24}O_6N_6S_2,C_2H_4O_2$ requires C, 50·15; H, 4·5; N, 16·7; S, 9·55%); sulphathiazole (0·5 g.), m. p. 268—270° (from alcohol) (Found: C, 46·35; H, 4·35; N, 12·6; S, 18·9. $C_{24}H_{24}O_6N_6S_4,C_2H_5{\cdot}OH$ requires C, 46·85; H, 4·5; N, 12·6; S, 19·2%).

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[*Received, June 4th*, 1957.]

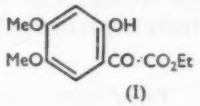
[a] Irani, *Current Sci.*, 1945, **14**, 46.

1022. *A New Synthesis of Abutic Acid.*

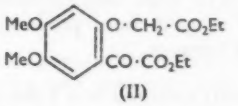
By K. R. HARGREAVES, A. MCGOOKIN, and ALEXANDER ROBERTSON.

AN investigation on the preparation of polyhydroxyphenylglyoxylic acids suggested an alternative route to the synthesis of abutic acid [1] (III; R = R′ = H), which is formed by the oxidation of rotenonic acid,[2] a degradation product of rotenone.

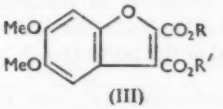
Prepared by the Hoesch reaction from ethyl cyanoformate and 3 : 4-dimethoxyphenol, ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate (I) was condensed with ethyl bromoacetate in potassium carbonate–acetone, yielding the ester (II) which on cyclisation with sodium ethoxide afforded ethyl hydrogen abutate (III; R = H, R′ = Et; or R = Et, R′ = H). Hydrolysis of this ester gave abutic acid, identical with the natural acid and forming methyl abutate,[1] identical with a specimen prepared from the natural acid.



(I)



(II)



(III)

Experimental.—Ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate. Interaction of 3 : 4-dimethoxyphenol (6 g.) and ethyl cyanoformate (6 ml.) by the Hoesch method gave a yellow crystalline

[1] Holton, Parker, and Robertson, *J.*, 1949, 2049.
[2] Takei, Miyajima, and Ono, *Ber.*, 1932, **65**, 1041.

product which separated overnight. This was washed well with ether and warmed on the steam-bath with water (30 ml.) for 20 min., and the resulting solid crystallised from ethanol, giving *ethyl* 2-*hydroxy*-4 : 5-*dimethoxyphenylglyoxylate* (6·5 g.) in pale yellow needles, m. p. 101°, sparingly soluble in light petroleum and having a green ferric reaction (Found: C, 56·9; H, 5·7. $C_{12}H_{14}O_6$ requires C, 56·6; H, 5·5%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate–light petroleum (b. p. 60—80°) in maroon needles, m. p. 172° (Found: N, 12·6. $C_{18}H_{18}O_9N_4$ requires N, 12·9%).

Ethyl 2-*ethoxycarbonylmethoxy*-4 : 5-*dimethoxyphenylglyoxylate* (II). A mixture of ethyl 2-hydroxy-4 : 5-dimethoxyphenylglyoxylate (3 g.), acetone (30 ml.), potassium carbonate (10 g.), and ethyl bromoacetate (2·5 g.) was refluxed until a sample did not give a ferric reaction (18 hr.). On isolation and crystallisation from alcohol the product gave *ethyl* 2-*ethoxycarbonylmethoxy*-4 : 5-*dimethoxyphenylglyoxylate* in needles (2 g.), m. p. 104°, soluble in ethyl acetate but insoluble in light petroleum (Found: C, 56·3; H, 6·0. $C_{16}H_{20}O_8$ requires C, 56·5; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 201°, from ethyl acetate (Found: N, 10·9. $C_{22}H_{24}O_{11}N_4$ requires N, 10·8%).

Abutic acid (III; R = H, R′ = H). The preceding ester (1·5 g.) in dry alcohol (50 ml.) containing sodium methoxide (from 0·15 g. of sodium) was heated under reflux for ¾ hr., filtered, poured into water (200 ml.), and acidified giving a flocculent precipitate of *ethyl hydrogen abutate* (1·1 g.) which crystallised from ethyl acetate in needles, m. p. 209°, soluble in acetone and sparingly soluble in alcohol or ethyl acetate (Found: C, 56·9; H, 5·0. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

This monoethyl ester (0·5 g.) was hydrolysed with hot 8% aqueous sodium hydroxide (5 ml.) for ½ hr. The resulting abutic acid separated from ethyl acetate in yellow needles (0·3 g.), m. p. 264°, undepressed on admixture with a natural specimen (Found: C, 54·3; H, 4·0. Calc. for $C_{12}H_{10}O_7$: C, 54·1; H, 3·8%). With ethereal diazomethane (10 mols.) for 2 hr. synthetical abutic acid gave the dimethyl ester (0·2 g.) which separated from methanol in needles, m. p. and mixed m. p. 156° (Found: C, 57·2; H, 5·0. Calc. for $C_{14}H_{14}O_7$: C, 57·1; H, 4·8%).

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1023. 17β-*Hydroxy*-17α-(3-*hydroxyprop*-1-*ynyl*)*androst*-4-*en*-3-*one*.

By (MISS) S. P. BARTON, G. COOLEY, B. ELLIS, and V. PETROW.

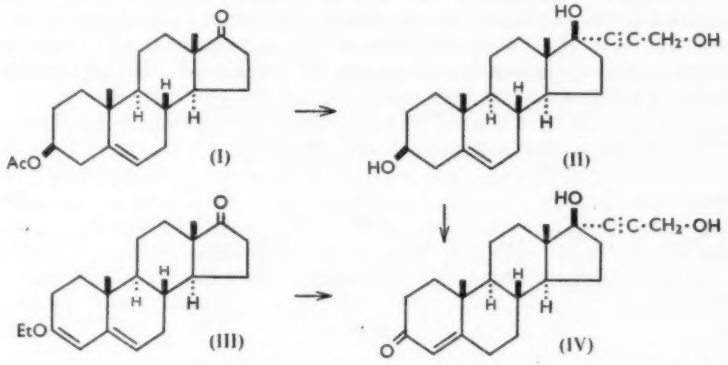
THE compound named in the title was required for biological study as a progestational agent. Condensation of 3β-acetoxyandrost-5-en-17-one (I) with propargyl alcohol in the presence of potassium *tert.*-amyloxide gave 17α-(3-hydroxyprop-1-ynyl)androst-5-ene-3β : 17β-diol (II) [cf. the conversion of 3β-hydroxyandrostan-17-one into 17α-(3-hydroxyprop-1-ynyl)androstane-3β : 17β-diol[1]], also obtained when 3β-(tetrahydro-2-pyranyl)-androst-5-en-17-one [2] was condensed with a Grignard reagent from propargyl tetrahydropyranyl ether [3] and the protective groups were removed from the resulting product. Under mild conditions compound (II) gave a diacetate, under more drastic conditions a triacetate.

Oppenauer oxidation of the triol (II) afforded an αβ-unsaturated ketone (IV). The survival of the primary alcohol group in the acetylenic substituent in these circumstances is noteworthy. Unequivocal confirmation of the structures follows from an alternative partial synthesis of compound (IV) from 3-ethoxyandrosta-3 : 5-dien-17-one (III) by condensation with the Grignard reagent from propargyl tetrahydropyranyl ether and removal of the protective 3- and 17-groups.

Experimental.—$[\alpha]_D$ refer to MeOH solutions in a 1-dm. tube. The ultraviolet absorption spectrum (in ethyl alcohol) was kindly determined by Mr. M. T. Davies, B.Sc.

[1] Wenner and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 24.
[2] Greenhalgh, Henbest, and Jones, *J.*, 1951, 1190; Ott, Murray, and Pederson, *J. Amer. Chem. Soc.*, 1952, **74**, 1239.
[3] Henbest, Jones, and Walls, *J.*, 1950, 3646; Conia, *Bull. Soc. chim. France*, 1955, 1449.

17α-(3-*Hydroxyprop*-1-*ynyl*)*androst*-5-*ene*-3β : 17β-*diol* (II). (*a*) Propargyl alcohol (13 g.) was added to a stirred solution of potassium (22·7 g.) in *tert.*-amyl alcohol (360 ml.) at 70°. When cool, the acetate (I) (23·5 g.) was added, and the mixture stirred for 2 hr. at room temperature and for 2½ hr. at 70°. The *triol* was isolated with ether and, purified from methanol–benzene, formed rods, m. p. 265° (decomp.), $[\alpha]_D^{25}$ −120° (*c* 0·32) (Found: C, 76·0; H, 9·1. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%). Treatment with acetic anhydride–pyridine at room temperature gave **3β-*acetoxy*-17α-(3-*acetoxyprop*-1-*ynyl*)*androst*-5-*en*-17β-*ol***, prisms (from



acetone–hexane), m. p. 131°, $[\alpha]_D^{25}$ −103° (*c* 0·4) (Found: C, 72·4; H, 8·5. $C_{26}H_{36}O_5$ requires C, 72·9; H, 8·5%), but at 100° in 22 hr. gave the *triacetate*, prisms (from acetone–hexane), m. p. 138—139°, $[\alpha]_D^{24}$ −92° (*c* 0·95) (Found: C, 71·4; H, 8·6. $C_{28}H_{38}O_6$ requires C, 71·5; H, 8·1%).

(*b*) A solution of propargyl tetrahydropyranyl ether (7·7 g.) in tetrahydrofuran (100 ml.) was added during 30 min. to a Grignard reagent prepared from magnesium (5 g.) and methyl iodide (20 ml.) in ether (120 ml.). After 30 min., 3β-(tetrahydro-2-pyranyl)androst-5-en-17-one (5 g.) in tetrahydrofuran (100 ml.) was added dropwise during ½ hr., after which the mixture was refluxed for 3½ hr. The complex was decomposed with aqueous ammonium chloride, and the product, isolated with ether, was heated under reflux for 25 min. with toluene-*p*-sulphonic acid (0·25 g.) in ethanol (50 ml.). The solid obtained on the addition of water was crystallised from aqueous pyridine, to give the triol (1·6 g.), identical with a sample prepared by method (*a*) above in m. p. (mixed m. p.) and optical rotation.

17β-*Hydroxy*-17α-(3-*hydroxyprop*-1-*ynyl*)*androst*-4-*en*-3-*one* (IV). (*a*) A solution of the triol (II) (7·2 g.) in toluene (900 ml.) and *cyclo*hexanone (240 ml.) was distilled until 200 ml. of distillate had collected. Aluminium *iso*propoxide (4 g.) in toluene (16 ml.) was then added, and the mixture refluxed for 1½ hr. The *product* was isolated in the usual way, and purified from acetone–hexane. It formed needles, m. p. 204—206°, $[\alpha]_D^{27}$ +3° (*c* 0·56) (Found: C, 77·4; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·1; H, 8·8%), $\lambda_{max.}$ 241 mμ (log ε 4·2).

(*b*) Propargyl tetrahydropyranyl ether (28 g.) in tetrahydrofuran (100 ml.) was slowly added to a Grignard reagent prepared from magnesium (6 g.) and ethyl iodide (20 ml.) in tetrahydrofuran (200 ml.). 30 Min. later, 3-ethoxyandrosta-3 : 5-dien-17-one (2·5 g.) in tetrahydrofuran (100 ml.) was added, and the mixture refluxed for 3 hr. When cool, it was treated with aqueous ammonium chloride and the product isolated with ether. The gummy material in ethanol (100 ml.) was refluxed for 1½ hr. with 2% aqueous oxalic acid (25 ml.), and the product isolated with ether. Chromatography on alumina (30 g.), with ether–benzene (3 : 2) as eluant, gave the ketone (1 g.), needles (from acetone–hexane), b. p. 204°, alone or mixed with a specimen prepared by method (*a*).

Treatment with acetic anhydride–pyridine for 18 hr. at room temperature gave a gum which failed to crystallise. Hydrolysis, however, converted this product into the diol (IV), identified by m. p. and mixed m. p.

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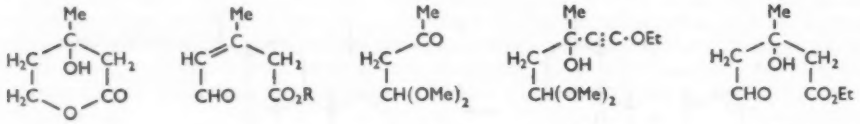
XUM

1024. *Studies in Relation to Biosynthesis. Part XII.* The Synthesis of Ethyl 4-Formyl-3-methylbut-3-enoate.*

By A. J. Birch, E. Pride, and Herchel Smith.

We recently suggested that mevalonic lactone (I), which is incorporated *in vitro* in high yield into cholesterol [2] and squalene [3] by systems prepared from rat livers, may function as the precursor of the *iso*pentane unit in natural products by initial conversion into the formyl acid (II; R = H). With the latter as basis a mechanistically plausible scheme for polyisoprenoid or carotenoid synthesis can be developed.[1] The suppression of the incorporation of labelled acetate into cholesterol by the acid (II; R = H) or an ester, readily hydrolysed to it by biological systems, would furnish support for the hypothesis. We have accordingly synthesised the ester (II; R = Et).



(I) (II) (III) (IV) (V)

4 : 4-Dimethoxybutan-2-one (III) and ethoxyethynylmagnesium bromide gave the carbinol (IV), which with dilute mineral acid gave, by hydrolysis of the acetal group and hydration of the triple bond, a product consisting largely of the hydroxy-ester (V). Distillation of this over a mixture of tartaric acid and aluminium phosphate afforded the ester (II; R = C_2H_5), whose structure follows from the light absorption [$\lambda_{max.}$ 228 mμ, ε 10,600 (as required for a ββ-disubstituted αβ-unsaturated aldehyde [4]); bands at 1735 and 1684 cm.$^{-1}$ (associated respectively with the saturated ester and αβ-unsaturated aldehyde groupings)].

Experimental.—1-*Ethoxy*-5 : 5-*dimethoxy*-3-*methylpent*-1-*yn*-3-*ol* (IV). 4 : 4-Dimethoxybutan-2-one [5] (10 g.) in tetrahydrofuran (50 c.c.) was added with stirring during 30 min. to ethoxyethynylmagnesium bromide [from ethoxyacetylene [6] (9·25 g.) and ethylmagnesium bromide (16·4 g.)] in tetrahydrofuran (100 c.c.) at 0° under nitrogen. The mixture was stirred at room temperature for 4 hr. and then added to ice-cold brine The organic layer was removed and the aqueous layer extracted with ether (3 × 100 c.c.). The combined organic solutions were washed with brine and dried ($MgSO_4$). Distillation and fractionation in a stream of nitrogen gave 1-*ethoxy*-5 : 5-*dimethoxy*-3-*methylpent*-1-*yn*-3-*ol*, b. p. 88°/0·6 mm. (Found: C, 59·6; H, 8·8. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%). The infrared spectrum had bands at 3480 (hydroxyl stretching) and 2275 cm.$^{-1}$ (C≡C stretching).

Ethyl 4-*formyl*-3-*methylbut*-3-*enoate* (II; R = Et). The ethoxypentynol (8 g.) was heated and shaken with 0·2N-sulphuric acid for 5 min. at 100°. The cooled solution was neutralised with sodium hydrogen carbonate and saturated with salt. The product was extracted with ether and heated at 160° (bath temp.) for 10 min. with anhydrous tartaric acid (0·4 g.) and aluminium phosphate [7] (0·4 g.) under slightly reduced pressure. Three distillations (two over a trace of aluminium phosphate) gave *ethyl* 4-*formyl*-3-*methylbut*-3-*enoate* (II; R = Et),

* Part XI, Birch and Massy-Westropp, *J.*, 1957, 2215.

[1] Birch, English, Massy-Westropp, and Smith, *Proc.*, 1957, 233.
[2] Tavormina, Gibbs, and Huff, *J. Amer. Chem. Soc.*, 1956, **78**, 4498.
[3] Cornforth, Cornforth, and Youhotsky-Gore, *Biochem. J.*, 1957, **66**, 10P; Dituri, Gurin, and Rabinowitz, *J. Amer. Chem. Soc.*, 1957, **79**, 79; Amdur, Rilling, and Bloch, *ibid.*, p. 2646.
[4] Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold & Co., London, 1954, p. 97.
[5] Royals and Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050.
[6] Eglington, Jones, Shaw, and Whiting, *J.*, 1954, 1860; Cope and Pike, *Org. Synth.*, 1954, **34**, 46.
[7] Cf. Fisher, *Ber.*, 1943, **76**, 734.

b. p. 67·5°/5 × 10^{-2} mm. (Found: C, 61·3; H, 7·9. $C_8H_{12}O_3$ requires C, 61·5; H, 7·8%), 2 : 4-*Dinitrophenylhydrazone*, m. p. 147° (from ethanol) (Found: C, 49·6; H, 4·9. $C_{14}H_{16}O_6N_4$ requires C, 50·0; H, 4·8%).

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UNIVERSITY OF MANCHESTER, MANCHESTER, 13. [*Received, July 19th*, 1957.]

1025. 4- *and* 6-*Methoxy*-2 : 3-*diphenylindole.*

By A. HILARY ORR and MURIEL TOMLINSON.

IT was assumed [1] that the product obtained by heating together benzoin, *m*-aminophenol, and *m*-aminophenol hydrochloride was 6- and not 4-hydroxy-2 : 3-diphenylindole, but no proof of this has yet been given. 7-Chloro-4-methoxy-2 : 3-diphenylindole has now been prepared from 2-chloro-5-methoxyaniline and benzoin, and removal of chlorine from this, by reduction, has given authentic 4-methoxy-2 : 3-diphenylindole, m. p. 147—148°, different from the methyl ether, m. p. 206—207°, obtained by methylation of the above hydroxyindole. The compound, m. p. 206—207°, must therefore be 6-methoxy-2 : 3-diphenylindole.

Experimental.—m-N-(α-*Phenylphenacyl*)*aminophenol*. *m*-Aminophenol (2 g.) and benzoin (4 g.) were heated in an oil-bath at 150—155° until effervescence ceased. The product crystallised in contact with acetic acid and was recrystallised from ethanol, giving m-N-(α-*phenylphenacyl*)*aminophenol* as needles, m. p. 137° (Found: C, 79·0; H, 5·5. $C_{20}H_{17}O_2N$ requires C, 79·2; H, 5·6%). This was unchanged when heated at 200° with either small quantities of hydrochloric acid or *m*-aminophenol hydrochloride, or when boiled in benzene with phosphoric oxide.

6-*Hydroxy*-2 : 3-*diphenylindole* (cf. Ballauf and Schmelzer [1]). Benzoin (5 g.), *m*-aminophenol (6 g.), and *m*-aminophenol hydrochloride (4 g.) were heated at 130—150°, under slightly reduced pressure, until effervescence ceased. Trituration with 10% sodium hydroxide solution afforded the sparingly soluble sodium salt of 6-hydroxy-2 : 3-diphenylindole which was collected, washed, and decomposed with dilute acetic acid. Recrystallisation from acetic acid gave needles, m. p. 145—148°, containing acetic acid which was completely removed only at about 200° (the loss in weight corresponds to ½ mol. of acetic acid). 6-Hydroxy-2 : 3-diphenylindole was left as a glass which, after being powdered, had m. p. 166—167° (Ballauf and Schmelzer report m. p. 168°) (Found: C, 84·3; H, 5·5. Calc. for $C_{20}H_{15}ON$: C, 84·2; H, 5·3%). Methylation was effected in refluxing acetone with 1 equiv. each of methyl sulphate and sodium hydroxide: 6-*methoxy*-2 : 3-*diphenylindole* crystallised from ethanol as prisms, m. p. 206—207° (Found: C, 84·2; H, 5·7. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%); it was unaffected by sodium hydroxide solution. Boiling the phenol with acetic anhydride and anhydrous sodium acetate for 15 min. afforded 6-*acetoxy*-2 : 3-*diphenylindole* which crystallised from acetic acid as needles, m. p. 190° (Found: C, 80·8; H, 5·2. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2%), and gradual addition of benzoyl chloride to a hot solution of the indole in aqueous potassium hydroxide gave 6-*benzoyloxy*-2 : 3-*diphenylindole* which separated from ethanol as needles, m. p. 158° (Found: C, 83·0; H, 5·1. $C_{27}H_{19}O_2N$ requires C, 83·3; H, 4·9%).

7-*Chloro*-4-*methoxy*-2 : 3-*diphenylindole*. 2-Chloro-5-methoxyaniline [2] (1 g.), benzoin (1·3 g.), and a drop of hydrochloric acid heated at 150° afforded 2-*chloro*-5-*methoxy*-N-(α-*phenylphenacyl*)*aniline* which crystallised from ethanol as needles, m. p. 104° (Found: C, 71·6; H, 5·0. $C_{21}H_{18}O_2NCl$ requires C, 71·4; H, 5·1%). Heated with one molar proportion of 2-chloro-5-methoxyaniline hydrochloride at 190°, this gave a gum which was washed with dilute hydrochloric acid and dissolved in benzene. The dried benzene solution was chromatographed on alumina, and the solid so obtained was extracted with hot methanol from which crystallised 7-*chloro*-4-*methoxy*-2 : 3-*diphenylindole* as needles, m. p. 129° (about 50%)

[1] Ballauf and Schmelzer, D.R.P., 533471.
[2] Cummins and Tomlinson, *J.*, 1955, 3475.

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(Found: C, 75·7; H, 4·9. $C_{21}H_{16}ONCl$ requires C, 75·6; H, 4·8%). A residue, which did not dissolve, was recrystallised from glacial acetic acid and yielded prisms, m. p. 275—278°, and was presumably αβ-*di*-(2-*chloro*-5-*methoxyanilino*)*stilbene* (Found: C, 68·9; H, 4·8. $C_{28}H_{24}O_2N_2Cl_2$ requires C, 68·4; H, 4·9%).

4-*Methoxy*-2 : 3-*diphenylindole*. A stream of hydrogen was passed through a mixture of 7-chloro-4-methoxy-2 : 3-diphenylindole (0·3 g.) and 10% palladium–charcoal (0·5 g.) in boiling mesitylene (75 c.c.) for 9 hr. The catalyst was then removed by filtration, the solvents were steam-distilled, and the remaining 4-*methoxy*-2 : 3-*diphenylindole* crystallised from ethanol as prisms, m. p. 147—148° (Found: C, 84·0; H, 5·6. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%).

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, July 22nd*, 1957.]

1026. *Spectroscopic Determination of the Stability of Naphthalene Picrate in Chloroform.*

By R. FOSTER.

THE stability constant of naphthalene picrate in chloroform was measured by Moore, Shepherd, and Goodall [1] by a partition method and, expressed as the association constant K = [naphthalene picrate]/([naphthalene][picric acid]), was 2·17 l./mole at 18°. This value is low because no account was taken of the solubility-depression effect of naphthalene in chloroform solution, which lowers the solubility of the picric acid. This effect was fully analysed by Anderson and Hammick,[2] and when it is taken into consideration K = 2·59 l./mole.

Recently Ross and Kuntz [3] determined this association constant spectroscopically by Andrews and Keefer's method [4] to be 0·99 l./mole at 25°. Ross and Kuntz [3] originally suggested that the difference between the spectroscopic and the partition value of K demanded the presence of at least two species of complex. The colorimetric method would measure a coloured complex, such as a charge-transfer complex, whereas the partition method would measure the sum of all types of interaction. Ross, Labes, and Schwarz [5] pointed out that spectroscopy should yield a constant which is the sum of the association constants of all types of association, so that both methods should give the same value for association constant.

Ross and Kuntz's determination, in which chloroform containing 0·75% of alcohol was used, was repeated by the same method, but with pure alcohol-free chloroform. The value of K = 1·1 l./mole at 19° agrees substantially with Ross and Kuntz's, but the method requires that the concentration of one of the components should be very large compared with that of the second. Ross and Kuntz made [naphthalene] $\gg$ [picric acid] and this condition was maintained here. If [picric acid] $\gg$ [naphthalene] complications arise because of the absorption due to the large concentration of free picric acid, and the necessary large but uncertain corrections make any results unreliable.

An important error in the spectroscopic method doubtless arises because the long-wavelength end of the picric acid absorption overlaps the absorption of the naphthalene picrate, in which region obviously the optical measurements must be made. Consequently any shift or alteration in intensity of the free picric acid may seriously affect quantitative measurements which involve the charge-transfer absorption of the complex. The solvent may cause such changes if large amounts of a third component (such as naphthalene) have to be added. In order to minimise these effects, it seems reasonable to take solutions with [naphthalene] = [picric acid]; estimations with this condition give K = 2·4 l./mole

[1] Moore, Shepherd, and Goodall, *J.*, 1931, 1447.
[2] Anderson and Hammick, *J.*, 1950, 1089.
[3] Ross and Kuntz, *J. Amer. Chem. Soc.*, 1954, **76**, 74.
[4] Andrews and Keefer, *ibid.*, 1952, **74**, 1891.
[5] Ross, Labes, and Schwarz, *ibid.*, 1956, **78**, 343.

at 19°, in good agreement with the partition value obtained by Moore, Shepherd, and Goodall.

Experimental.—Materials. "AnalaR" chloroform was washed ten times with distilled water, dried over successive amounts of calcium chloride, and fractionated immediately before use (n_D^{20} 1·4456). Picric acid, recrystallised four times from alcohol, had m. p. 122°. B.D.H. naphthalene, "pure for molecular-weight determinations," was used without further purification (m. p. 80·2°).

Method. If x = molar concentration of the complex (assumed to be 1 : 1, there being no evidence for other species) and A = molar concentration of the picric acid and of the naphthalene originally added then:

$$K = x/(A - x)^2 \doteq x/(A^2 - 2Ax) \text{ if } x \text{ is small}$$

If D is the optical density and ε the extinction coefficient, at a particular wavelength, of the molecular complex then

$$K = \frac{D/\varepsilon}{A^2 - (2AD/\varepsilon)} \text{ or } \frac{A}{D} = \frac{1}{A}\left(\frac{1}{K\varepsilon}\right) + \frac{2}{\varepsilon} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

For a 1 : 1 complex, a plot of A/D against $1/A$ as abscissa should be linear with intercept $2/\varepsilon$ and gradient $1/K\varepsilon$. This is a simplified version of the method used by Ross and Labes.[6]

For $K \approxeq 2$ l./mole, $x/A \approxeq 0{\cdot}1$ at $A = 0{\cdot}05$M and $x/A \approxeq 0{\cdot}01$ at $A \doteq 0{\cdot}005$M: also we have $\varepsilon_{\text{picric acid}}/\varepsilon_{\text{naphthalene picrate}} \approxeq 0{\cdot}01$ or less at $\lambda \geqslant 420$ mμ. So the measured values of optical density ($\bar{D}$) can be converted into the corrected values (D), corresponding to the absorption due to the complex alone, by subtracting an optical density value (δD) equivalent to the picric acid originally added. These values are obtained from the experimentally confirmed Beer's-law relationships for picric acid alone in chloroform at the various wavelengths used (420—460 mμ). The derived extinction coefficients are given in Table 2.

TABLE 1. *Determination of K from measurements at 420 mμ.*

10^3A(M)	$\bar{D}$	δD	D	$1/A$	A/D	10^3A(M)	$\bar{D}$	δD	D	$1/A$	A/D
54·44	2·123	0·263	1·860	18·4	0·0293	23·82	0·563	0·115	0·448	42·0	0·0532
40·83	1·425	0·198	1·227	24·5	0·0333	20·41	0·429	0·099	0·330	49·0	0·0618
34·02	1·001	0·165	0·836	29·4	0·0407	17·01	0·323	0·082	0·241	58·8	0·0706
30·62	0·882	0·148	0·734	32·7	0·0417	13·61	0·215	0·066	0·149	73·5	0·0913
27·33	0·714	0·132	0·582	36·7	0·0467	10·20	0·134	0·049	0·085	98·0	0·1200

By least-mean-squares from cols. 5 and 6, eqn. (1) becomes $A/D = 0{\cdot}00531 + 0{\cdot}00157(1/A)$ whence $\varepsilon = 377$ and $K = 2{\cdot}29$ l./mole.

TABLE 2. *Summarised results.*

Temp.	Wavelength (mμ)	$\varepsilon_{\text{picric acid}}$	$\varepsilon_{\text{complex}}$	K (l./mole)
19°	420	4·84	377	$2{\cdot}2_9$
19	430	0·152	279	$2{\cdot}5_6$
19	440	0·052	221	$2{\cdot}3_9$
19	450	0·024	152	$2{\cdot}4_6$
19	460	0·014	108	$2{\cdot}2_7$

Mean value for the association constant of naphthalene–picric acid in chloroform at 19° = 2·4 l./mole.

Individual naphthalene and picric acid solutions were made up separately and appropriate volumes taken to make an equimolar solution. This was diluted to make the individual solutions. Optical measurements were made on solutions in 1 cm. stoppered fused silica cells by using a Unicam S.P. 500 spectrophotometer. Full details of one determination are given in Table 1. All the plots of A/D against $1/A$ give good straight lines. The results are summarised in Table 2.

This work was carried out during the tenure of an Edward A. Deeds Fellowship of the University of St. Andrews.

QUEEN'S COLLEGE (UNIVERSITY OF ST. ANDREWS), DUNDEE. [*Received, July 31st,* 1957.]

[6] Ross and Labes, *J. Amer. Chem. Soc.*, 1957, **79**, 76.

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INTERNATIONAL ATOMIC WEIGHTS, 1957.

[*Reprinted from the Report of the Commission on Atomic Weights in the* Comptes rendus *of the 19th Conference of the International Union of Pure and Applied Chemistry*, 1957.]

Alphabetical order.

Name.	Symbol.	Atomic No.	Atomic weight.	Name.	Symbol.	Atomic No.	Atomic weight.
Actinium	Ac	89	—	Mercury	Hg	80	200·61
Aluminium	Al	13	26·98	Molybdenum	Mo	42	95·95
Americium	Am	95	—	Neodymium	Nd	60	144·27
Antimony	Sb	51	121·76	Neon	Ne	10	20·183
Argon	A *	18	39·944	Neptunium	Np	93	—
Arsenic	As	33	74·91	Nickel	Ni	28	58·71
Astatine	At	85	—	Niobium	Nb	41	92·91
Barium	Ba	56	137·36	Nitrogen	N	7	14·008
Berkelium	Bk	97	—	Nobelium	No	102	—
Beryllium	Be	4	9·013	Osmium	Os	76	190·2
Bismuth	Bi	83	209·00	Oxygen	O	8	16
Boron	B	5	10·82	Palladium	Pd	46	106·4
Bromine	Br	35	79·916	Phosphorus	P	15	30·975
Cadmium	Cd	48	112·41	Platinum	Pt	78	195·09
Cæsium	Cs	55	132·91	Plutonium	Pu	94	—
Calcium	Ca	20	40·08	Polonium	Po	84	—
Californium	Cf	98	—	Potassium	K	19	39·100
Carbon	C	6	12·011	Praseodymium	Pr	59	140·92
Cerium	Ce	58	140·13	Promethium	Pm	61	—
Chlorine	Cl	17	35·457	Protactinium	Pa	91	—
Chromium	Cr	24	52·01	Radium	Ra	88	—
Cobalt	Co	27	58·94	Radon	Rn	86	—
Copper	Cu	29	63·54	Rhenium	Re	75	186·22
Curium	Cm	96	—	Rhodium	Rh	45	102·91
Dysprosium	Dy	66	162·51	Rubidium	Rb	37	85·48
Einsteinium	Es	99	—	Ruthenium	Ru	44	101·1
Erbium	Er	68	167·27	Samarium	Sm	62	150·35
Europium	Eu	63	152·0	Scandium	Sc	21	44·96
Fermium	Fm	100	—	Selenium	Se	34	78·96
Fluorine	F	9	19·00	Silicon	Si	14	28·09
Francium	Fr	87	—	Silver	Ag	47	107·880
Gadolinium	Gd	64	157·26	Sodium	Na	11	22·991
Gallium	Ga	31	69·72	Strontium	Sr	38	87·63
Germanium	Ge	32	72·60	Sulphur	S	16	32·066†
Gold	Au	79	197·0	Tantalum	Ta	73	180·95
Hafnium	Hf	72	178·50	Technetium	Tc	43	—
Helium	He	2	4·003	Tellurium	Te	52	127·61
Holmium	Ho	67	164·94	Terbium	Tb	65	158·93
Hydrogen	H	1	1·0080	Thallium	Tl	81	204·39
Indium	In	49	114·82	Thorium	Th	90	232·05
Iodine	I	53	126·91	Thulium	Tm	69	168·94
Iridium	Ir	77	192·2	Tin	Sn	50	118·70
Iron	Fe	26	55·85	Titanium	Ti	22	47·90
Krypton	Kr	36	83·80	Tungsten	W	74	183·86
Lanthanum	La	57	138·92	Uranium	U	92	238·07
Lead	Pb	82	207·21	Vanadium	V	23	50·95
Lithium	Li	3	6·940	Xenon	Xe	54	131·30
Lutetium	Lu	71	174·99	Ytterbium	Yb	70	173·04
Magnesium	Mg	12	24·32	Yttrium	Y	39	88·92
Manganese	Mn	25	54·94	Zinc	Zn	30	65·38
Mendelevium	Md	101	—	Zirconium	Zr	40	91·22

* The International Table uses the symbol Ar for argon but this has not been adopted by The Chemical Society.

† Because of natural variations in the relative abundance of the isotopes of sulphur the atomic weight of this element has a range of ±0·003.

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EDITORIAL REPORT ON NOMENCLATURE, 1957.*

Definitive rules of nomenclature for inorganic chemistry, a further large section of the definitive rules of nomenclature for organic chemistry, definitive rules of nomenclature of steroids, and tentative rules of nomenclature of vitamin B_{12} were approved at the meeting of the International Union of Pure and Applied Chemistry at Paris in 1957, and their publication is expected during 1958. Until this publication becomes available and has been considered by The Chemical Society these new rules will not be discussed in these Editorial Nomenclature Reports. The Editor may, however, be able to provide guidance to those concerned with specialised aspects.

In view of these forthcoming publications, and for other reasons, nomenclature in the Society's publications during 1957 has been mainly on established lines. The problems that have arisen have been mostly of specialist interest, but the following few points may be mentioned here.

(1) The term " double-bonding ligand " indicates a ligand which possesses a strong σ-bond and also a strong π-bond. The terms " π-bonding ligand " and " σ-bonding ligand " refer to ligands which form bonds deriving their strength mainly from π-bonds and σ-bonds respectively. This distinction between the σ-bond strengths of ligands possessing π-bonds in addition is important in discussions of stabilities and of directive effects in complex compounds. Thus the " *trans*-directing " properties of the ligands CO, PCl_3, PF_3, C_2H_4, methyldiphenylarsine, and *o*-phenylenebisdimethylarsine are all fairly high, but the relative stabilities of platinum(II) compounds involving these ligands differ markedly with respect to heat, moisture, and excess of ligand (*J.*, 1957, 2018).

(2) A nomenclature generally adaptable for mesoionic compounds (sydnones, etc.) is badly needed but not yet in sight. In the meanwhile, use of the prefix ψ is probably the best available (cf. *J.*, 1957, 1556) when trivial names such as sydnone do not exist.

(3) Problems in stereochemistry arise with increasing frequency. Solutions (perhaps only temporary) of three problems during the year may find analogous uses.

(*a*) It was necessary to distinguish the three stereoisomeric 1 : 5-dichloroanthraquinone dioximes (*J.*, 1957, 1901). The terms *syn* and *anti* were used to describe the mutual stereochemical relations of the oxime groups, and *cis* and *trans* to describe the configurations of these groups with respect to the nearer chlorine atom.

(*b*) In a paper dealing with cyclitol derivatives (*J.*, 1957, 3691) the most satisfactory method of designating the (absolute) configuration at each asymmetric centre was the *R*, *S* symbolism (Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81) but this obscured the *cis-trans*-relations which are the characteristic feature of this field. The solution adopted was to use the customary inositol-type of nomenclature supplemented by the *R* or *S* symbol for the lowest-numbered asymmetric centre. This method is capable of wide application.

(*c*) A situation arose where conversion of a sugar into its alcohol introduced an additional element of symmetry in such a way that strict application of nomenclature rules obscured the chemical relations. D-Ribitol 5-phosphate is the same substance as L-ribitol 1-phosphate. According to the standard rules of nomenclature, the name with the lower number should have preference, *i.e.*, L-ribitol 1-phosphate. Nevertheless, D-ribitol 5-phosphate was used in the paper (*J.*, 1957, 1870) because of its use in previous papers and because the substance is probably related metabolically to D-ribose 5-phosphate and D-ribulose 5-phosphate and is degraded to D-glyceric acid. Moreover, it was important to avoid the possible implication that L-ribitol 1-phosphate is in any way related to L-α-glycerophosphoric acid. These two compounds are, in fact, in stereochemically opposite series. The correct name for the naturally occurring

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* Reprints of this Report and of those for each of the years 1950—1956 (except 1952, which is out of print) may be obtained from the General Secretary, The Chemical Society, price 1*s.* each (post free).

L-α-glycerophosphoric acid, according to standard rules of nomenclature, is D-glycerol 1-(dihydrogen phosphate) (equivalent to the 3-phosphate). However, probably for reasons concerning its biochemical origin, the L-α or L-3 nomenclature has always been adopted for this compound.

(4) Attention is directed to two bad practices which are becoming increasingly common in chemical papers. One is the loose use of words ending in " lysis ". Lysis denotes fission; " heterolytic fission " is a tautological phrase. In fact, great care is needed in use of " lysis." In chemistry it means " fission by ", *e.g.*, electrolysis, hydrolysis, solvolysis, pyrolysis. Homolysis and heterolysis are exceptions, for they denote fission of a bond *in* an electronically symmetrical and asymmetrical manner, respectively. But in biochemistry and biology the term lysis usually denotes fission *of*, *e.g.*, amylolytic, carcinolysis, lipolysis, plasmolysis. In chemical papers the chemical usage of " fission *by* " should be adhered to. Better, such terms should be restricted to well-established ones or to cases where no simple alternative is available: words such as chlorinolysis and diazomethanolysis are pure jargon. And the use of, *e.g.*, acetolysis to denote fission *of* an acetate group is inexcusable.

A second is tautological use of such words as reaction, process, etc., as in " reduction process ", " hydrogenation reaction ".

INTERNATIONAL ATOMIC WEIGHTS, 1957.

Order of atomic numbers.

Atomic No.	Name.	Symbol.	Atomic weight.
1	Hydrogen	H	1·0080
2	Helium	He	4·003
3	Lithium	Li	6·940
4	Beryllium	Be	9·013
5	Boron	B	10·82
6	Carbon	C	12·011
7	Nitrogen	N	14·008
8	Oxygen	O	**16**
9	Fluorine	F	19·00
10	Neon	Ne	20·183
11	Sodium	Na	22·991
12	Magnesium	Mg	24·32
13	Aluminium	Al	26·98
14	Silicon	Si	28·09
15	Phosphorus	P	30·975
16	Sulphur	S	32·066 *
17	Chlorine	Cl	35·457
18	Argon	A †	39·944
19	Potassium	K	39·100
20	Calcium	Ca	40·08
21	Scandium	Sc	44·96
22	Titanium	Ti	47·90
23	Vanadium	V	50·95
24	Chromium	Cr	52·01
25	Manganese	Mn	54·94
26	Iron	Fe	55·85
27	Cobalt	Co	58·94
28	Nickel	Ni	58·71
29	Copper	Cu	63·54
30	Zinc	Zn	65·38
31	Gallium	Ga	69·72
32	Germanium	Ge	72·60
33	Arsenic	As	74·91
34	Selenium	Se	78·96
35	Bromine	Br	79·916
36	Krypton	Kr	83·80
37	Rubidium	Rb	85·48
38	Strontium	Sr	87·63
39	Yttrium	Y	88·92
40	Zirconium	Zr	91·22
41	Niobium	Nb	92·91
42	Molybdenum	Mo	95·95
43	Technetium	Tc	—
44	Ruthenium	Ru	101·1
45	Rhodium	Rh	102·91
46	Palladium	Pd	106·4
47	Silver	Ag	107·880
48	Cadmium	Cd	112·41
49	Indium	In	114·82
50	Tin	Sn	118·70
51	Antimony	Sb	121·76
52	Tellurium	Te	127·61
53	Iodine	I	126·91
54	Xenon	Xe	131·30
55	Cæsium	Cs	132·91
56	Barium	Ba	137·36
57	Lanthanum	La	138·92
58	Cerium	Ce	140·13
59	Praseodymium	Pr	140·92
60	Neodymium	Nd	144·27
61	Promethium	Pm	—
62	Samarium	Sm	150·35
63	Europium	Eu	152·0
64	Gadolinium	Gd	157·26
65	Terbium	Tb	158·93
66	Dysprosium	Dy	162·51
67	Holmium	Ho	164·94
68	Erbium	Er	167·27
69	Thulium	Tm	168·94
70	Ytterbium	Yb	173·04
71	Lutetium	Lu	174·99
72	Hafnium	Hf	178·50
73	Tantalum	Ta	180·95
74	Tungsten	W	183·86
75	Rhenium	Re	186·22
76	Osmium	Os	190·2
77	Iridium	Ir	192·2
78	Platinum	Pt	195·09
79	Gold	Au	197·0
80	Mercury	Hg	200·61
81	Thallium	Tl	204·39
82	Lead	Pb	207·21
83	Bismuth	Bi	209·00
84	Polonium	Po	—
85	Astatine	At	—
86	Radon	Rn	—
87	Francium	Fr	—
88	Radium	Ra	—
89	Actinium	Ac	—
90	Thorium	Th	232·05
91	Protactinium	Pa	—
92	Uranium	U	238·07
93	Neptunium	Np	—
94	Plutonium	Pu	—
95	Americium	Am	—
96	Curium	Cm	—
97	Berkelium	Bk	—
98	Californium	Cf	—
99	Einsteinium	Es	—
100	Fermium	Fm	—
101	Mendelevium	Md	—
102	Nobelium	No	—

* Because of natural variations in the relative abundance of the isotopes of sulphur the atomic weight of this element has a range of ±0·003.

† The International Table uses the symbol Ar for argon but this has not been adopted by The Chemical Society.

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XUM

XUM

XUM